Study Title

Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats

Volume 1 of 2

TEST GUIDELINES: U.S. EPA Health Effects Test Guidelines
OPPTS 870.3650 (2000)

OECD Guideline for the Testing of Chemicals
Section 4: Health Effects, Number 422 (1996)

AUTHOR: Linda A. Malley, Ph.D., D.A.B.T.

STUDY COMPLETED ON: October 29, 2004

PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
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LABORATORY PROJECT ID: DuPont-12690

WORK REQUEST NUMBER: 14294

SERVICE CODE NUMBER: 1422

SPONSOR: American Chemistry Council
1300 Wilson Boulevard
Arlington, Virginia 22209
U.S.A.

SPONSOR STUDY NUMBER: OLF-92.0-HPV789-DHL

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are consistent with the OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98)17 except for the item documented below. The item listed does not impact the validity of the study.

A sample of the test substance was not retained at Haskell Laboratory due to its potential to form peroxides. Since peroxide formation can result in an explosive hazard, the remaining test substance and empty container were safely discarded after the report was completed.

Applicant: E.I. du Pont de Nemours and Company
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Study Director: Linda A Malley 29 Oct 2004

Linda A. Malley, Ph.D., D.A.B.T. Date
Senior Research Toxicologist
E.I. du Pont de Nemours and Company

QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

25430

Dates of Inspections:

Protocol:	March 25, 2003
Conduct:	April 14, 19, 21, 23, 25, 2003; May 8, 21, 27, 2003
Records, Reports:	July 11, 21-22, 2003; August 5, 21-22, 25-28, 2003; October 7, 9, 10, 2003

Dates Findings Reported to:

Study Director:	March 25, 2003; April 14, 21, 23, 25, 2003; May 8, 21, 27, 2003; July 11, 22, 2003; August 27, 28, 2003; October 14, 2003
Management:	April 14, 21, 23, 25, 2003; May 12, 21, 27, 2003; June 10, 2003; July 11, 22, 2003; August 1, 2003; September 11, 24, 2003; October 14, 21, 2003

Reported by: Kimberly B. Brebner 27-OCT-2004

Kimberly B. Brebner
Staff Quality Assurance Auditor

Date

CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of data obtained from this study.

Analytical Evaluation by: Janet C. Maslanka — 29-Oct-2004
Janet C. Maslanka, B.S.
Senior Staff Chemist — Date

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Statistical Analysis by: John W. Green — 29-Oct-2004
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Issued by Study Director: Linda A Malley 29-Oct-2004

Linda A. Malley, Ph.D., D.A.B.T. Date
Senior Research Toxicologist

This report was accepted by the Sponsor

Sponsor: 10/26/04

Elizabeth J. Moran, Ph.D., D.A.B.T. Date
Sponsor Representative

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STUDY INFORMATION

CA Index Name: Naphtha (petroleum), light steam-cracked, debenzenized, C8-16-cycloalkadiene concentrate

Synonyms/Codes:
Dicyclopentadiene/Codimer Concentrate
DCPD/Codimer Concentrate
DCP 97
H-25430
121302 (Lot No.)

Haskell Number: 25430

CAS Registry Number: 68478-10-4

Composition:

29.175 wt %	endo- and exo-DCPD
18.726 wt %	C4-MCPD and C5-MCPD codimers
13.210 wt %	MCPD dimer
12.903 wt %	CPD-MCPD codimer
8.129 wt %	C8 aliphatic and aromatic hydrocarbons
7.144 wt %	C4-CPD and C5-CPD codimers
3.625 wt %	MCPD-C7 dimer
2.771 wt %	Tetrahydroindene
1.917 wt %	Trimers
0.927 wt %	C7 cyclic hydrocarbon
0.697 wt %	C5 acyclic hydrocarbon dimer
0.634 wt %	MCPD monomer
0.078 wt %	CPD monomer
0.063 wt %	C6 acyclic hydrocarbons

Physical Characteristics: Colorless liquid

Stability: The test substance appeared to be stable under the conditions of the study.

Sponsor: American Chemistry Council
1300 Wilson Boulevard
Arlington, Virginia 22209
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Study Initiated/Completed: March 26, 2003 / (see report cover page)

STUDY PERSONNEL

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Analytical Chemist (Test Substance Characterization Evaluation):	Vladimir Čapka, Ph.D.
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SUMMARY

Groups of 12 young, adult, male or nulliparous female Crl:CD®(IGS)BR rats were administered an oral daily dose of 0, 5, 25, or 100 mg/kg/day Dicyclopentadiene/Codimer Concentrate (DCPD/Codimer Concentrate) for 29 or 30 days, respectively. Satellite groups of 12 young, nulliparous female rats were administered an oral, daily dose of 0, 5, 25, or 100 mg/kg/day during a premating period of 2 weeks, a cohabitation period of 2 weeks, a gestation period of approximately 3 weeks, and a lactation period of approximately 3 days. Body weights and clinical signs were recorded throughout the study. Food consumption was recorded weekly for subchronic females and during the premating period for males. After approximately 30 days, blood samples were collected from all male rats and all subchronic female rats for measurement of hematology, coagulation, and clinical chemistry parameters. A neurobehavioral test battery, consisting of motor activity and functional observational battery assessments, was conducted on all male rats and subchronic female rats during pretest and again following approximately 4 weeks of test substance administration. On test days 30 and 31, respectively, all male rats and all subchronic females underwent gross necropsy. Selected tissues from the control and 100 mg/kg/day groups, and target organs from all groups were processed for histopathology and examined.

Following the 2-week premating period, each satellite female was paired with a male of the same respective dosage group. Measurements of body weight and clinical signs of toxicity in satellite females were conducted throughout premating, cohabitation, gestation, and lactation. Food consumption was measured in satellite females during gestation and lactation. On postpartum day 4, lactating females and nonpregnant females were sacrificed, selected organs were weighed, and selected tissues were evaluated microscopically in females that did not produce a litter. Offspring were counted, weighed, and clinical observations recorded on days 0, 1, and 4 of lactation and were sacrificed on postnatal day 4.

There were no adverse, test substance-related clinical signs of toxicity in males, subchronic females, or satellite females administered any dosage of the test substance. Unscheduled mortality did not occur at any dosage in males, subchronic females, or satellite females.

Decreased weight gain was observed in 25 and 100 mg/kg/day subchronic females. However, since body weight was only 3% and 4% lower than the control values on test day 29 in 25 and 100 mg/kg/day subchronic females, respectively, and since there were no effects on body weight gain in satellite females, the decreased body weight gain was not considered to be biologically adverse. There were no effects on body weight or weight gain in males.

There were no test substance-related or statistically significant effects on food consumption or food efficiency in males, subchronic females, or satellite females administered any dosage of the test substance.

No test substance-related effects or statistically significant differences in mating index, fertility index, gestation length, number of implantation sites, implantation efficiency, pre-implantation

loss, post-implantation loss, or number of *corpora lutea* were observed for any dosage of the test substance in satellite females.

There were no test substance-related effects on mean pup weight, number of pups born, number of pups born alive, sex ratio, gestation index, external abnormalities, or litter survival for postnatal days 0-4 in the offspring from any dosage group.

There were no test substance-related effects observed in any neurobehavioral parameter for males or subchronic females administered any dosage of the test substance.

There were no adverse changes in hematological, coagulation, or clinical chemistry parameters in male or subchronic female rats. Administration of 100 mg/kg/day of the test substance for approximately 30 days resulted in decreased serum bilirubin concentration. However, decreased serum bilirubin concentration is considered to be secondary to enzyme induction as a pharmacological response to a xenobiotic and was not considered adverse.

Administration of 5, 25, or 100 mg/kg/day of the test substance for approximately 30 days produced a dose-related increase in renal tubular hyaline droplets in male rats which was correlated with an increase in the incidence of bilateral pale kidney discoloration, and with changes in kidney weight parameters. Increased hyaline droplets were not observed in females, although 100 mg/kg/day subchronic females had a slight increase in kidney weight parameters which was biologically insignificant. The hyaline droplet accumulation in male rats was not considered to be an adverse effect of the test substance. Also, renal tubular hyaline droplet accumulation is species and sex specific, and is not predictive of an effect on other species.

Hepatocellular hypertrophy, and associated increases in liver weight parameters were observed in 100 mg/kg/day males, subchronic females, and in satellite females. One subchronic female in the 25 mg/kg/day group also had hepatocellular hypertrophy. However, hepatocellular hypertrophy is considered to be secondary to enzyme induction as a pharmacological response to a xenobiotic, and was not considered to be adverse.

Thyroid follicular cell hypertrophy was observed in 25 and 100 mg/kg/day males and females, and was considered to be test substance-related and potentially adverse.

No morphological changes were detected in reproductive tissues for the satellite females administered any dosage of the test substance.

The no-observed-effect level (NOEL) was not determined for males based on increased incidence of renal tubular hyaline droplets at all dosages, and, therefore, the low-observed-effect level (LOEL) level was 5 mg/kg/day, the lowest dosage tested. However, since hyaline droplets are not considered to be relevant for humans, the no-observed-adverse-effect level (NOAEL) for males was 5 mg/kg/day. The NOEL and NOAEL in females was 5 mg/kg/day based on thyroid follicular cell hypertrophy at 25 mg/kg/day. The LOEL in females was, therefore, 25 mg/kg/day.

The NOEL and NOAEL for reproductive parameters was considered to be 100 mg/kg/day based on the absence of effects on mating index, fertility index, gestation length, number of

implantation sites, implantation efficiency, pre-implantation loss, post-implantation loss, or number of *corpora lutea* at any dosage.

The NOEL and NOAEL for developmental toxicity was considered to be 100 mg/kg/day based on the absence of effects in offspring at any dosage.

The NOEL and NOAEL for neurobehavioral parameters was considered to be 100 mg/kg/day in males and females based on the absence of effects at any dosage.

Parameters	NOEL (mg/kg/d)	NOAEL (mg/kg/d)	LOEL (mg/kg/d)
Systemic	Nd[a] M 5 F	5 M 5 F	5 M 25 F
Reproductive (M/F)	100	100	-
Developmental (pups)	100	100	-
Neurobehavioral	100 M/F	100 M/F	-

a ND denotes not determined.
M = males; F = females

INTRODUCTION

Dicyclopentadiene/Codimer Concentrate (DCPD/Codimer Concentrate) was evaluated for potential toxicity using a combined repeated dose toxicity/reproduction/developmental toxicity study. The purpose of this study was to evaluate the potential effects of DCPD/Codimer Concentrate when administered by gavage to male and female rats for a minimum of 28 consecutive days. General toxicity, clinical pathology, neurobehavioral activity, gross pathology, and histopathology were evaluated.

In addition, a satellite group was used to evaluate the potential effects of DCPD/Codimer Concentrate during premating (approximately 2 weeks), gestation (approximately 3 weeks), and lactation through day 4. In the satellite group, gonadal function, mating behavior, fertility, implantation, development of the conceptus, parturition, gross pathology, and histopathology were evaluated.

Prior to conducting the main study, a range-finding study was conducted in time-mated pregnant female rats.(1) Dose levels for the main study were selected based on the results of the range-finding study.

STUDY DESIGN

A. Treatment Groups and Dose Levels

Main Subchronic[a]				Satellite[b]		Dosage
Group Male	Number of Males	Group Female	Number of Females	Group Females	Number of Females	mg/kg/day
I	12	II	12	II-0	12	0 (Control)
III	12	IV	12	IV-0	12	5 (Low)
V	12	VI	12	VI-0	12	25 (Medium)
VII	12	VIII	12	VIII-0	12	100 (High)

a Main study males and females (repeated-treatment, general toxicity, neurotoxicity, clinical pathology, and pathology endpoints)

b Satellite females (reproductive and developmental toxicity endpoints)

MATERIALS AND METHODS

A. Test Guidelines

The study design complies with the following test guidelines:

- Office of Prevention, Pesticides and Toxic Substances (OPPTS) U.S. Environmental Protection Agency (EPA) (2000). OPPTS 870.3650 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. *Health Effects Test Guidelines*.

- Organisation for Economic Co-Operation and Development (OECD) (1996). 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. *Guideline for the Testing of Chemicals*.

B. Route of Administration

The test substance was administered by oral intubation (gavage) to ensure maximal exposure and provide for comparison with other similar substances that have or will be tested by oral administration. The vehicle control substance was also administered by oral gavage. The degree of the test substance or vehicle absorption by the test system was deemed beyond the scope and objectives of the study.

C. Duration of the Study

The study initiation date was defined as the day the study protocol was signed by the Study Director. The experimental start date was defined as the first day of dosing (test day 1). The experimental termination date of the main study was defined as the final day of sacrifice at Haskell Laboratory. The completion date of the study is defined as the date the final report is signed by the Study Director at Haskell Laboratory.

D. Test Substance

1. Identification:

Chemical Name:	Dicyclopentadiene/Codimer Concentrate
Other Name Used in this Protocol:	DCPD/Codimer Concentrate
CAS Registry Number:	68478-10-4
Haskell Sample Number:	25430
Lot Number:	121302
Purity:	100%
Color:	colorless
Form:	Liquid
Supplier for DCPD:	ExxonMobil
Vehicle:	Corn oil
Supplier for Corn Oil:	Mazola®
Lot Number for Corn Oil:	26-FEB-04

The test substance was supplied as a liquid and stored at or below 70ºF and protected from light and air.

2. Characterization

The test substance was characterized by the Haskell Laboratory Analytical Chemistry Group (see Appendix B) prior to the start of the range-finding study.

3. Stability

Stability of the neat test substance was established by analyses at 2 time points. Aliquots were taken after the end of the range-finding study, which served as the beginning of the study analysis for the main study, and near the end of the main study. The results of the analyses were reported as test substance stability[2,3] (Appendices D and E). The stability samples were analyzed by gas chromatography (GC) using flame ionization detection (FID). A peak of the major component was compared to an internal standard to determine a ratio. A calibration curve was prepared from this ratio, and samples were evaluated based on the calibration curve.

E. Vehicle

Corn oil was used as test substance vehicle. The corn oil was purchased from reliable commercial vendors by Haskell Laboratory and was not expected to contain any contaminants

that would interfere with the conduct of the study. The corn oil was assumed to be stable under the conditions of the study, and was stored refrigerated.

F. Degree of Absorption

For the purposes of this study, clinical signs of toxicity and other manifestations of toxic effects were considered to indicate uptake of the test substance. No attempt was made to establish the actual systemic dose each rat received. All treatment-related effects were therefore reported as a function of the administered dose(s).

G. Dosing Formulation Preparation, Sampling, and Analysis

Dosing formulations of the test substance were prepared daily with corn oil by adding the corn oil to the measured amount of test substance and stirring to establish uniformity.

Near the beginning of the study, 4 samples (approximately 3 mL per sample) were collected from each formulation, and were analyzed for homogeneity/concentration verification, and 5-hour stability in the vehicle at room temperature. Near the middle and end of the dosing period, duplicate samples were taken from all formulations and analyzed for concentration verification.

The remaining formulation samples after dosing were stored refrigerated, and discarded when the final results from the analysis were accepted. Whenever samples were collected, a sample of the vehicle was also collected and analyzed.

1. Sample Submittal

On test day 2 (April 10, 2003), dosing formulations containing DCPD/Codimer Concentrate at the concentrations of 2.5, 12.5, and 50 mg/mL were collected. These samples were analyzed to determine homogeneity/concentration verification and 5-hour room temperature stability. Dosing formulations from the same levels were collected on test day 13 (April 21, 2003) and test day 37 (May 15, 2003) and were analyzed for concentration verification. A 0 mg/mL (control) sample was collected and submitted with each sampling.

All dosing formulation samples were collected on the same day the formulations were prepared. They were analyzed when received or when reanalysis was necessary.

2. Recovery Sample Analysis

Concurrent with dosing formulation analyses, recovery of DCPD/Codimer Concentrate from spiked Mazola® corn oil was tested at the low-level (2.5 mg/mL), at the mid-level (12.5 mg/mL), and at the high-level (50 mg/mL) to confirm the analytical method. DCPD/Codimer Concentrate was weighed into 100 mL volumetric flasks and diluted with 3 mL of Mazola® corn oil. All recovery samples were then mixed for dispersion of the DCPD/Codimer Concentrate in the corn oil. The samples were then processed and analyzed in the same manner as the dosing samples at similar concentrations.

3. Dosing Formulation Treatment

Each dosing sample (3 mL) was mixed with 10 mL chloroform to dissolve the Mazola® corn oil, and then diluted to 100 mL with hexane and mixed to dissolve the DCPD/Codimer Concentrate in the formulation. The dosing samples were further diluted with hexane to the expected concentrations of approximately 0.06, 0.075, and 0.15 mg/mL (of the primary component) prior to analysis. Before all final dilutions, the internal standard (refer to Calibration and Quantitation Section) at the approximate concentration of 0.03 mg/mL and the 0 mg/mL sample (initial dilution) were added to each test sample to give an equivalent final concentration of the matrix (corn oil diluted with chloroform/hexane) and internal standard in all samples.

4. Chromatographic Conditions

Instrument:	Hewlett-Packard Model 6890 GC
Column:	DB-1, 30 m x 0.25 mm ID, 0.25 µm film thickness
Injector:	Split, 180°C
Detector:	FID; 280°C
Carrier Gas:	Helium (2.7 mL/min)
Split ratio:	10:1
Injection Volume:	3 microliter
Oven Program:	Gradient
Initial Temperature:	50°C
Initial Time:	1.0 min.
Level 1 Rate:	20°C/min.
Level 1 Temperature:	250°C
Level 1 Time:	2.00 min.
Total run time:	13.00 min.

5. Calibration and Quantitation

A separate sample of the test substance, DCPD/Codimer Concentrate (H-25430), was used as the analytical reference standard for the analysis. A stock solution was prepared in hexane. Calibration solutions of approximately 0.03 to 0.24 mg/mL were prepared in hexane from this solution. A stock solution of the internal standard (toluene, 99.5% pure) was prepared in hexane and added to each calibration standard and test solution to give a final concentration of approximately 0.03 mg/mL. Before all final dilutions, the 0 mg/mL sample (initial dilution) was added to each solution to give an equivalent final concentration of the matrix (corn oil diluted with chloroform/hexane) in all standards. The ratio of the peak height for DCPD isomer #2 and for the internal standard from replicate GC analysis of these solutions was used to construct a calibration curve by least squares regression. Measured concentrations for the samples were determined by applying the peak height ratios from replicate injections of each sample to the calibration curve.

Test substance homogeneity/uniformity in the vehicle was evaluated by calculating the coefficient of variation (C.V. = standard deviation/mean x 100) of the measured concentrations in the top, middle, and bottom samples (homogeneity) or duplicate samples (concentration

verification) for each dosing level. A coefficient of variation of less than or equal to 10% is the standard criterion at Haskell Laboratory for acceptable distribution of the test substance throughout the formulation.

The mean result of the homogeneity samples or concentration verification duplicate samples for each dosing level was used to determine the concentration of the test substance for the respective dosing levels.

Stability was evaluated by using the mean result of the homogeneity samples as the baseline for comparing the corresponding stability results.

H. Test System

Fifty-six male and 112 female Crl:CD®(SD)IGS BR rats (nulliparous) were obtained from Charles River Laboratories, Inc., Raleigh, North Carolina. The rats were approximately 8-10 weeks old at study start. Body weight ranged from 172.0 – 286.4 g on test day 1. The Crl:CD®(SD)IGS BR rat was selected on the bases of extensive experience with this strain at Haskell Laboratory and its suitability with respect to longevity, sensitivity, and low incidence of spontaneous diseases.

I. Animal Husbandry

1. Identification

Each rat was assigned a unique 6-digit Haskell animal number and an individual cage identification number. After assignment to groups, the last 3 digits of the Haskell animal number were tattooed on the tail of each rat. The Haskell animal number and cage identification number were both included on the cage label.

2. Housing Environment

Rats were housed singly in stainless steel, wire-mesh cages, suspended above cage boards, except as described in the next 2 paragraphs. Each cage rack contained only rats of one gender.

During cohabitation, males designated for subchronic toxicity were cohoused with the satellite females in their respective groups until evidence of copulation was observed.

Females in the satellite group were housed in polycarbonate pans with bedding (Bed-o-Cobs®) from gestation day 19 or the end of the cohabitation period (if evidence of copulation was not detected) until sacrifice.

Animal rooms were targeted at a temperature of 22 ± 4°C and a relative humidity of 40%-60%. Animal rooms were artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle.

3. Food and Water

All rats were provided tap water (United Water Delaware) *ad libitum*. They were fed PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 (chunk chow) *ad libitum*.

4. Animal Health and Environmental Monitoring Program

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.

Food samples are analyzed for total bacterial, spore, and fungal counts.

Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal food was used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program was administered by the attending laboratory animal veterinarian. Evaluation of these data did not indicate any conditions that affected the validity of the study.

J. Quarantine and Pretest Procedures

Upon arrival at Haskell Laboratory, all rats were housed 1 per cage, sexes separate, in quarantine. The rats were:

- quarantined for a minimum of 6 days.
- identified temporarily by cage identification.
- weighed at least 3 times during quarantine.
- observed with respect to weight gain and any gross signs of disease or injury during the entire 12-day pretest period.

The rats were released from quarantine by the laboratory animal veterinarian designee on the bases of acceptable body weights and clinical signs.

K. Assignment to Groups

Rats of each sex were selected for use on study on the bases of adequate body weight gain and freedom from any clinical signs of disease or injury. They were distributed by computerized, stratified randomization into study groups as designated in the Study Design, so that there were no statistically significant differences among group body weight means within a sex. To the extent possible, the weight variation on test day 1 did not exceed ± 20% of the mean for each sex.

After assignment to groups, each rat was housed individually.

Rats that were not assigned to a test group were released for other laboratory purposes or sacrificed by carbon dioxide asphyxiation and discarded without pathological evaluation, at the discretion of the study director.

L. Dose Selection

In a range-finding study,[1] 6 time-mated, presumed pregnant female rats per group were administered DCPD/Codimer Concentrate once daily by gavage at dosages of 0, 25, 100, or 500 mg/kg/day during gestation days 12-19.

Dose-related reductions in maternal body weight, body weight gain, and/or food consumption occurred in rats administered 25, 100, or 500 mg/kg/day. Body weight loss occurred on days 12-18G for females dosed with 500 mg/kg/day, and decreased body weight gain persisted for the remainder of the study in females dosed with 500 mg/kg/day. During days 12-18G, food consumption values for rats in the 500 mg/kg/day group were less than 10 g per day.

One female in the 500 mg/kg/day group was sacrificed *in extremis* on gestation day 17 due to substantial body weight loss, and a prolonged period of not eating. This female was pregnant. Maternal animals in the 500 mg/kg/day group had clinical signs of dehydration, abnormal gait or mobility (described as an arched back while walking on tip toes), diarrhea, hunched over posture, feet retracted during handling, hypersensitivity, and wet and/or stained fur. In addition, rats in the 500 mg/kg/day group had a small spleen size and enlarged adrenals.

Mortality did not occur at 100 mg/kg/day or below. Wet and/or stained fur was also noted in 1 animal in the 100 mg/kg/day group.

There were no effects on number of litters produced, early or late resorptions, implantations, *corpora lutea*, live fetuses, or dead fetuses in any dosage group.

A dose-related trend for reduced fetal weights (3%, 6%, 22%) was observed in the 25, 100, and 500 mg/kg/day groups, respectively. In addition, placental weight was reduced in the 500 mg/kg/day group. There were no fetal external malformations or variations observed in any dose group. Based on these effects in the range-finding study, the dosages selected by the sponsor for the main study were 0, 5, 25, and 100 mg/kg/day.

M. Administration of Dosing Formulations

The test substance was administered once daily by gavage at a dose volume of 2 mL/kg. Females designated for the subchronic toxicity study (main group) were dosed for 30 days. Females designated for the reproduction study (satellite group) were dosed during the premating period (approximately 2 weeks), the mating period until evidence of copulation was observed (up to 2 weeks), the gestation period (approximately 3 weeks), and days 0-4 of lactation (if delivery was in progress at the time of dosing, the female was not administered the dose). Females showing no evidence of copulation continued to be dosed after the end of the cohabitation period until sacrifice. Males were dosed during the premating period (approximately 2 weeks), during the mating period until evidence of copulation was observed, and subsequently until sacrifice (29 days total). Control rats were dosed with corn oil (2 mL/kg). Dosages were based on the most recently recorded weight.

N. Clinical Observations and Mortality

1. Predosing Observations

At the time of dosing, each rat was individually handled and examined for abnormal behavior and appearance.

On each dosing day, predosing clinical signs were collected approximately 24 hours following the preceding dose (except on test day 1) and represent effects of the test substance that were still present 24 hours after the preceding dose.

2. Postdosing Observations

During the test period, cage-site examinations to detect moribund or dead rats and abnormal behavior and/or appearance among rats were conducted at least twice daily throughout the study. One of the cage-site examinations occurred in the afternoon, at least 1-2 hours after dosing had been completed. Abnormal clinical observations were noted by exception.

Postdosing clinical signs were considered to represent acute effects of the test substance. Since the animal was not removed from the cage for this evaluation, enduring signs, such as alopecia, were not visible to the observer, and were not recorded.

3. Detailed Observations

During the pretest period and on days 8, 15, 22, 29, each rat designated for subchronic toxicity was individually handled and examined for abnormal behavior and appearance in a standardized arena. The detailed clinical observations included (but were not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or bizarre behavior. Any abnormal clinical observations were recorded. Animals that did not exhibit clinical signs of toxicity were recorded as “no abnormality detected” (NAD) in the study records.

Detailed clinical observations were considered to represent enduring clinical signs present after 8, 15, 22, and 29 days of dosing.

O. Body Weights and Body Weight Gains

1. Subchronic Toxicity Animals

All rats were weighed on days 1, 8, 15, 22, and 29 and at scheduled sacrifice. In addition, rats undergoing functional observational battery and motor activity evaluations were weighed on the days of those observations.

2. Satellite Animals - Premating and Cohabitation Periods

Female rats were weighed on days 1, 8, and 15 of the premating period and weekly during the cohabitation period.

3. Satellite Animals - Gestation and Lactation Periods

Female rats were weighed daily during gestation, on the day of delivery (day 0 postpartum), and on the day of sacrifice (day 4 postpartum). Weights collected on gestation days other than 0, 7, 14, and 21 were used to calculate dosages, and were not included in the summary tables.

P. Food Consumption and Food Efficiency

The amount of food consumed by each rat over the weighing interval was determined by weighing each feeder at the beginning of the interval and subtracting the diet remaining and the amount of spillage from the feeder at the end of the interval. From these determinations, mean daily food consumption (g/day) was calculated. Mean food efficiency was calculated by dividing the amount of weight gain by the amount of food consumed for a given interval of test days.

1. Subchronic Toxicity Animals

Food consumption was determined on days 1, 8, 15, 22, and 29 (food consumption in males was discontinued upon cohabitation).

2. Satellite Animals - Premating and Cohabitation Periods

Food consumption was determined on days 1, 8, and 15 of the premating period for female rats. Food consumption was not determined during cohabitation.

3. Satellite Animals - Gestation and Lactation Periods

Food consumption was determined on gestation days 0, 7, 14, and 21, and on days 0 and 4 of lactation for female rats.

Q. Neurobehavioral Evaluations

Prior to initiation of dosing, all rats designated for subchronic toxicity and approximately 8 extra rats per sex were evaluated to establish their baseline FOB parameters. The FOB was performed again on the male and female rats designated for subchronic toxicity on test days 29 and 30, respectively. The week 4 assessment for males was conducted approximately 23-26 hours after the dose was administered on test day 28 and was conducted before the dose was administered on test day 29. The week 4 assessment for females was conducted approximately 23-26 hours after the dose was administered on test day 29, and was conducted before the dose was administered on test day 30.

In order to accommodate the Neurotoxicology testing facility, the functional observational battery (FOB) and motor activity (MA) assessments were conducted in 2 replicates per sex over a 2-day period for baseline and a 2-day period for the week 4 FOB. Replicate designations were not reported in the final report, but were recorded in the study records. Assignment to a given replicate was counterbalanced across all groups within a sex.

For all the following assessments, the experimenter was unaware of the group designation of the animal.

1. Functional Observational Battery (FOB)

FOB testing consisted of a series of quantified behavioral observations conducted in a sequence that proceeded from the least interactive to the most interactive.

During the FOB assessments, each rat was evaluated in 3 "environments:" 1) inside the home cage; 2) upon removal from the home cage and while being handled; and 3) in a standard "open field" arena (approximately 85 x 59 x 20 cm). The animal's actual home cage was not amenable to transport between the housing room and neurobehavioral laboratory areas. Therefore, for the purposes of the FOB, the "home cage" was defined as the cage on the transport rack to which an individual animal was assigned and to which the rats had been acclimated and undisturbed for a period of at least 10 minutes.

Inside the home cage, the presence of the following was recorded, if and when observed:

- palpebral closure
- writhing
- circling
- biting
- unusual changes in body posture
- gait/coordination

During removal from the home cage and handling, each rat was assessed for:

- fur appearance
- ease of removal
- ease of handling
- muscle tone
- the presence of
  - vocalizations
  - piloerection
  - bite marks
  - palpebral closure
  - lacrimation
  - exophthalmus
  - salivation

In the open field arena, the rats was evaluated for:

- unusual responses in
  - arousal
  - grooming
  - gait/coordination
  - posture
  - rate of respiration
  - ease of respiration
  - righting reflex
  - the number of rearing movements
- the presence of
  - convulsions
  - tremors
  - muscle fasciculation
  - muscle spasms
  - diarrhea
  - polyuria
  - palpebral closure
  - vocalizations

While in the standard arena, simple assessments of sensory function were made, including:

- response to
  - approach/touch
  - auditory stimulus
  - tail pinch

The presence or absence of pupillary constriction assessed after a beam of light was directed into each eye (pupillary constriction) was measured immediately prior to removing the rats from the motor activity chambers because the darkened room in which the apparatus was located facilitated observing the response. The presence of diarrhea and polyuria on the cage boards below the motor activity cages was also evaluated following each motor activity session.

The remainder of FOB testing involved standardized or calibrated devices. Fore- and hindlimb grip strength were measured by a strain gauge device (Chatillon® -Digital Force gauge) (3 trials per animal per session). Hindlimb splay was assessed by inking the hind paws and releasing the rat from a height of approximately 32 cm onto a piece of paper that covered a padded surface. Heel-to-heel distance was measured from the inked impressions and recorded.

Rectal body temperature was measured with a YSI Precision™ 4000 Thermometer and temperature probe.

2. Motor Activity (MA)

Motor activity sessions were conducted on the same animals, the same day as FOB assessments, following the FOB assessments. Rats were individually tested in one of 30 nominally identical, automated activity monitors (Coulbourn®). Groups were counterbalanced across the monitors and time of day to the fullest extent possible. The infrared monitoring device enabled measurement of 2 dependent variables, duration of movement and number of movements. A continuous movement was counted as one movement regardless of duration. Each test session was 60 minutes in duration, and the results were expressed for the total session, total motor activity over a 60-minute time period, as well as for 6 successive 10-minute blocks.

3. Test Facilty Positive Control Data

Procedures and data describing the effects of acrylamide, carbaryl, d-amphetamine, and trimethyltin are presented in 5 separate reports.[4,5,6,7,8] These positive control studies are the basis of training certification for the people making judgments in the neurobehavioral and neuropathology tests. The data also document that the equipment and procedures are capable of detecting effects that may be seen in neurotoxicity studies of this type.

R. Clinical Pathology Evaluation

A clinical pathology evaluation was conducted on all animals designated for subchronic toxicity 30 (males) or 31 (females) days after initiation of the study. These animals were fasted after 3 p.m. (at least 15 hours) the day prior to sacrifice. Blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each animal while the animal was under carbon dioxide anesthesia. Blood samples for coagulation parameters were collected at sacrifice from the abdominal *vena cava* of each animal while the animal was under carbon dioxide anesthesia. Additional blood collected from the *vena cava* was placed in a serum tube, processed to serum, and frozen at -80°C. Serum was discarded without analysis because further tests were not required to support experimental findings. Bone marrow smears were prepared at sacrifice from all surviving animals. Bone marrow smears were stained with Wright's stain, but analysis was not necessary to support experimental findings.

1. Hematology and Coagulation

Blood samples were evaluated for quality by visual examination prior to analysis. Complete blood counts, including reticulocytes, were determined on a Bayer® Advia 120 hematology analyzer or determined from microscopic evaluation of the blood smear. Wright-stained blood smears from all animals were examined microscopically for confirmation of automated results and evaluation of cellular morphology. Blood smears, stained with new methylene blue, were prepared from each animal undergoing a hematology evaluation, but were not needed for examination. Coagulation times were determined on a Sysmex® CA-1000 Coagulation Analyzer.

The following hematology and coagulation parameters were determined:

red blood cell count platelet count

hemoglobin	white blood cell count
hematocrit	differential white blood cell count
mean corpuscular volume	microscopic blood smear examination
mean corpuscular hemoglobin	
mean corpuscular hemoglobin concentration	
red cell distribution width	prothrombin time
absolute reticulocyte count	activated partial thromboplastin time

2. Clinical Chemistry

Serum clinical chemistry parameters were determined on a Roche Diagnostics (BMC)/Hitachi® 717 clinical chemistry analyzer.

The following clinical chemistry parameters were determined:

aspartate aminotransferase	glucose
alanine aminotransferase	total protein
sorbitol dehydrogenase	albumin
alkaline phosphatase	globulin
total bilirubin	calcium
urea nitrogen	inorganic phosphorus
creatinine	sodium
cholesterol	potassium
triglycerides	chloride

S. Breeding

1. Start of Cohabitation

After 2 weeks of treatment with the test substance, each satellite female was cohoused on a 1:1 basis with a randomly selected subchronic male of the same treatment level in the male's cage.

2. Duration of Cohabitation Period

On the day copulation was confirmed (designated as day 0 of gestation), the satellite female was transferred back to individual cage housing. Mating pairs were cohoused until evidence of copulation was observed, or until 2 weeks had elapsed.

3. Evidence of Copulation

During the breeding period, daily vaginal lavage samples were evaluated for the presence of sperm. The presence of a vaginal copulation plug *in situ* or sperm in vaginal lavage was considered evidence of copulation.

T. Gestation Procedures

After being transferred into polycarbonate pans (on day 19 of gestation for mated females, or at the end of the cohabitation period for females without evidence of copulation), female rats were observed at least twice daily for signs of delivery and pups.

U. Lactation Procedures

The day when delivery was complete was designated day 0 postpartum. At each examination period, pups were individually handled and examined for abnormal behavior and appearance; any dead, missing, or abnormal pups were recorded. Any pups found dead or that were euthanized in moribund condition were examined to the extent possible and discarded.

1. Day 0 Postpartum

Live and dead pups in each litter were counted as soon as possible after delivery was completed. Live pups in each litter were individually weighed and sex determined. Any clinical abnormalities in pups were recorded.

2. Day 1 Postpartum

Pups in each litter were counted by sex and individually weighed. Any clinical abnormalities in pups were recorded.

3. Day 4 Postpartum

Pups in each litter were counted by sex and individually weighed. Any clinical abnormalities (e.g. external alterations) in pups were recorded. All offspring were euthanized by decapitation.

V. Anatomic Pathology Evaluation

1. Rats Designated for Subchronic Toxicity

On test days 30 and 31 for males and females, respectively, groups of 12 male and 12 female rats from the 0, 5, 25, and 100 mg/kg/day groups were sacrificed and necropsied. The 48 male rats in this main study were also used as the P_1 males in the Reproductive/Developmental Toxicity Screening Test discussed below.

Rats scheduled for sacrifice were fasted overnight on the afternoon before their scheduled sacrifice. The order of sacrifice for scheduled deaths was random among all treatment groups. Rats were euthanized by carbon dioxide anesthesia and exsanguination. Gross examinations were performed on all male and female rats.

The following tissues were collected from subchronic toxicity rats.

Digestive System[a]
- liver
- esophagus
- stomach
- duodenum
- jejunum
- ileum
- cecum
- colon
- rectum
- tongue
- pancreas

Urinary System
- kidneys
- urinary bladder

Respiratory System
- lungs
- trachea
- nose
- pharynx/larynx

Cardiovascular System
- heart
- aorta

Hematopoietic System
- spleen
- thymus
- mediastinal lymph node
- mandibular lymph node
- mesenteric lymph node
- bone marrow [b]

Endocrine System
- pituitary gland
- parathyroid gland
- thyroid gland
- adrenal glands

Nervous System
- brain (three sections)
- spinal cord (three levels)
- eyes (with optic nerve)
- sciatic nerve

Musculoskeletal System
- femur/knee joint
- sternum
- skeletal muscle

Reproductive System

Male
- testes
- epididymides
- prostate
- seminal vesicles
- coagulating glands

Female [c]
- ovaries (with oviducts)
- cervix
- uterus
- vagina

Integumentary System
- skin
- salivary glands
- lacrimal glands
- mammary gland [d]

Miscellaneous
- gross observations [e]

a Including Peyer's patches
b Bone marrow was collected with the femur and sternum.
c Females in the satellite groups were examined for the presence and number of uterine implantation sites and ovarian *corpora lutea.*
d Females only
e Gross observations made at necropsy for which histopathology was not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) were generally not collected.

The following tissues were weighed from rats sacrificed by design in the 28-day subchronic toxicity study: liver, kidneys, lungs, adrenal glands, thymus, spleen, brain, heart, testes, epididymides, ovaries, and uterus. Organ weight/final body weight and organ weight/brain weight ratios were calculated.

Gross lesions that were diagnosed at necropsy for which microscopic examination was not appropriate (e.g., fluid accumulation, ruffled fur, missing anatomic parts) were generally not collected. Gross lesions for which a microscopic diagnosis would not be additive (e.g. osteoarthritis, pododermatitis, chronic dermatitis of the tail, urinary calculi, and deformity of the teeth, toe, tail, or pinna) were saved but were generally not processed for microscopic evaluation.

Testes, epididymides, and eyes were fixed in Bouin's solution. All other tissues were fixed in 10% neutral buffered formalin. Processed tissues were embedded in paraffin, sectioned approximately 5-6 microns thick, stained with hematoxylin and eosin (H&E), and examined microscopically by a veterinary pathologist.

All collected tissues from subchronic toxicity study rats from control and 100 mg/kg/day rats received a full histopathological examination. Liver, thyroid gland, gross lesions, and kidney (males only) were examined from the 5 and 25 mg/kg/day subchronic toxicity study rats.

2. Rats Designated for Reproductive Evaluations

a. P_1 Adults

P_1 adults included the male rats from the subchronic toxicity study (main study) and a separate population of satellite female rats that included 12 rats per dose level. P_1 males (Groups I, III, V, and VII) received gross and microscopic examinations as described for the subchronic toxicity study. All satellite females (Groups II-0, IV-0, VI-0, and VIII-0) received a gross pathological examination that included recording the number of ovarian *corpora lutea* and uterine implantation sites. Rats were sacrificed by carbon dioxide anesthesia and exsanguination.

The same tissues collected from female rats in the subchronic toxicity study were collected from the satellite females at necropsy. Tissue fixation and processing were also the same as for the subchronic study. Microscopic evaluation of the satellite female rats was limited to the reproductive organs of the 5 females with impaired reproductive performance, including 2 Group II-0 rats (Animal Numbers 671776 and 671795), 1 Group VI-0 rat (Animal Number 671749), and 2 Group VIII-0 rats (Animal Numbers 671752 and 671777).

Similarly, the reproductive organs from the P_1 males that cohabited with these females were also examined. All tissues from the Group I rats (Animal Numbers 671688 and 671709) and the Group VII rats (Animal Numbers 671686 and 671692) were examined as prescribed for the subchronic toxicity study. Only the reproductive organs of the Group V rat (Animal Number 671680) were examined. The gross and microscopic findings of the P_1 males are included in the subchronic toxicity tables and appendices.

Satellite female rats had the following organs weighed at necropsy: brain, liver, kidneys, lungs, ovaries, and uterus. Organ weight/final body weight and organ weight/brain weight ratios were calculated.

W. Data Analyses

1. Reproductive Function Calculations

The following table lists the indices of reproductive functions that were calculated for the P_1 adults.

Mating Index (%)	=	$\frac{\text{Number Copulated}^{a}}{\text{Number Cohabited}}$	x 100
Fertility Index (%)	=	$\frac{\text{Number Pregnant}^{b}}{\text{Number Copulated}^{a}}$	x 100
Gestation Index (%)	=	$\frac{\text{Number of Litters with at Least One Live Pup}}{\text{Number of Litters}}$	x 100
Implantation Efficiency (%)[c]	=	$\frac{\text{Number of Pups Born}}{\text{Number of Implantation Sites}}$	x 100
Pups Born Alive (%)[c]	=	$\frac{\text{Number of Pups Born Alive}}{\text{Number of Pups Born}}$	x 100
Viability Index (%)[c,d]	=	$\frac{\text{Number of Pups Alive Day 4}}{\text{Number of pups born alive}}$	x 100
Preimplantation Loss[e]	=	$\frac{\text{Number of } \textit{corpora lutea} - \text{Number of implantation sites}}{\text{Number of } \textit{corpora lutea}}$	
Postimplantation Loss[e]	=	$\frac{\text{Number of implantation sites} - \text{Number of pups}}{\text{Number of implantation sites}}$	

a Evidence of copulation = intravaginal or cageboard copulatory plug and/or sperm in vaginal lavage sample, found dead pregnant, or delivery of a litter.
b Including those found dead pregnant during gestation.
c Determined for each litter. Mean and standard deviation for each dose level were calculated.
d Excluding litters sacrificed due to death of dam during lactation.
e Restricted to pregnant dams.

2. Summary Data for Body Weight, Weight Gain, Food Consumption, and Food Efficiency

Body weight data for subchronic males, subchronic females, and satellite females were summarized weekly. Body weight gain data for subchronic males were summarized over weekly intervals, and for the intervals of days 1-15, 15-29, and 1-29 so that any potential effects from cohabitation on these parameters could be evaluated. Food consumption and food efficiency for subchronic males were summarized for the intervals of test days 1-8, 8-15, and 1-15. Body weight gain, food consumption, and food efficiency data for subchronic females and satellite

females were summarized over weekly intervals and for test days 1-29 (subchronic females), test days 1-15 of premating (satellite females), test days 0-21 of gestation (satellite females), and test days 0-4 of lactation (satellite females).

3. Statistical Methods

<table>
<tr><th rowspan="2">Parameter</th><th rowspan="2">Preliminary Test</th><th colspan="2">Method of Statistical Analysis</th></tr>
<tr><th>If preliminary test is not significant</th><th>If preliminary test is significant</th></tr>
<tr><td rowspan="3">Body Weight
Body Weight Gain
Food Consumption
Gestation Length
Implantation Site Numbers
Implantation Efficiency
Mean Number of Pups per Litter
Percent Born Alive
0-4 Day Viability
Viability Index
Number of Corpora Lutea
Sex Ratio
Pre-implantation Loss
Post-implantation Loss
Organ Weights</td><td>Test for lack of trend[9]</td><td>Sequential application[10] of the Jonckheere-Terpstra trend test[11]</td><td>Preliminary tests for pairwise comparison</td></tr>
<tr><td colspan="2">OR[a]</td></tr>
<tr><td>Levene’s test for homogeneity[12] and Shapiro-Wilk test[13] for normality[b]</td><td>One-way analysis of variance[14] followed with Dunnett's test[15, 16, 17]</td><td>Kruskal-Wallis test[18] followed with Dunn's test[19]</td></tr>
<tr><td>Food Efficiency</td><td>None</td><td colspan="2">One-way analysis of variance[14] followed with Dunnett's test[15]</td></tr>
<tr><td>Incidence of Clinical Observations
Incidence of FOB Descriptive Parameters
Mating Index
Fertility Index
Gestation Index</td><td>None</td><td colspan="2">Cochran-Armitage test for trend[14]c</td></tr>
<tr><td>Clinical Pathology[d]</td><td>Levene’s test for homogeneity[12] and Shapiro-Wilk test[13] for normality[b]</td><td>One-way analysis of variance[14] followed with Dunnett's test[15, 16, 17]</td><td>Kruskal-Wallis test[18] followed with Dunn's test[19]</td></tr>
<tr><td>Mean Pup Weights (Covariates: litter size, sex ratio)</td><td>None</td><td>Linear contrast of the least square means[20]</td><td>None</td></tr>
</table>

a Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.

b If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed with Dunn’s test.

c If the incidence was not significant, but a significant lack of fit occurred, then Fisher’s Exact test[21] with a Bonferroni correction was used.

d When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that data. When an individual observation was recorded as being greater than a certain value, calculations were performed on the recorded value. For example, if specific gravity was reported as >1.083, 1.083 was used for any calculations performed with that data.

a. Neurobehavioral Data
(Appendix GG)

- Statistical Analysis of Motor Activity

Motor activity (number and duration of movements) is done by repeated measures ANOVA[22] with day and bin (epoch) as repeated factors, with bin nested within day, possibly after a normalizing, variance stabilizing transformation. Since bin has more than 2 levels, consideration must be given to the variance-covariance structure in testing for significance of treatment effects overall or within a single day or bin. Where the correlations between observations on the same subject in different bins on the same day appear to vary as separation in time increases (a real possibility), either a Huynh-Feldt or Greenhouse-Geisser adjustment is made or an alternative variance-covariance structure (e.g., unstructured,[20] auto-regressive,[23] heterogeneous auto-regressive,[23] or heterogeneous compound symmetry[20]) is used that reflects this varying correlation. Assessment of the need for such an adjustment or alternative variance-covariance structure can be done using Mauchly's criterion[24] for sphericity, through inspection of the sample variance-covariance matrix, or through the use of variance-covariance diagnostics described in Hocking *et al.,*[25] Green and Hocking,[23] Grynovicki and Green,[26] and Searle *et al.*[27]

The responses are assessed for normality using the Shapiro-Wilk[13] test applied to the residuals from the ANOVA model and appropriate plots. If the data are judged non-normal, then a normalizing transformation is sought. If no such transformation can be found, then separate analyses for the responses from each day and bin are done. If no normality problem is found or is resolved by a transformation, then Levene's test[12] for variance homogeneity is done. If significant variance heterogeneity is found from this test and appropriate plots, then a normalizing, variance-stabilizing transformation is sought. If none is found, then separate analyses for the responses from each day and bin are done.

In the context of this repeated measures ANOVA, linear contrasts[28] are estimated to determine treatment effects. A linear contrast for dose trend is estimated as are individual comparisons of treatments to control. This is done on each day, averaging across bins, and in each bin. To control the false positive rate associated with these comparisons, adjustments to the p-values are made based on the significance (or lack thereof) of the Dose-by-Day and Dose-by-Day-by-Bin interactions, and the test for linear trend in the dose-response.

In addition, a repeated measures analysis is done of the daily sums over bins of the responses from each animal. Such sums (or, equivalently so far as conclusions are concerned, averages) are more likely to be normally distributed than are the individual responses, so that separate analyses by each time point are less likely. These data are analyzed by the same method described below for grip strength.

- Statistical Analysis of Grip Strength, Foot Splay, Body Temperature, and Rearing

These endpoints are analyzed by repeated measures ANOVA with day as the only repeated factors, possibly after a normalizing, variance stabilizing transformation. Since day has only two

levels, the Greenhouse-Geisser[29] conditions are automatically satisfied and no special treatment of the variance-covariance matrix or the tests for treatment effects is needed. Normality and variance homogeneity are evaluated as above, analogous actions are taken where significant non-normality or variance heterogeneity is encountered, and tests for treatment effects are conducted as above, except that bin is not a consideration.

b. Trend Test

For each parameter analyzed with a trend test, the test was applied to the data sequentially. If a significant dose-response was detected, data from the top dose group was excluded and the test repeated until no significant trend was detected.[10]

c. Litter Parameters

For litter parameters, the proportion of affected fetuses per litter or the litter mean was used as the experimental unit for statistical evaluation.[30]

d. Level of Significance

The level of significance selected was $p < 0.05$ for trend tests Levene's, Shapiro-Wilk, Kruskal-Wallis, Dunn's, and linear contrasts. Where the data were tied and the standard large sample version of Jonckheere's test[11] was not applicable, exact p values were calculated using permutation methodology.[31]

RESULTS AND DISCUSSION

Test Substance Characterization

A. Test Substance Characterization
(Appendix B)

Characterization of DCPD/Codimer Concentrate test substance was performed by Gas Chromatography (GC) with Flame-Ionization Detection (FID). The composition of the test substance was determined as follows:

Component	Composition
3a, 4, 7, 7a-Tetrahydroindene	2.67 ± 0.04%
Dicyclopentadiene	30.8 ± 0.2%
Unidentified Components Above 0.1%	65.2%
Other Unidentified Components Below 0.1%	1.60%

Analytical Evaluation of Dosing Formulations (Appendix C)

A. Chromatography for Dosing Formulations
(Appendix C)

DCPD/Codimer Concentrate (based on DCPD isomer #2) eluted from the GC column as a resolved peak with a retention time of approximately 4.0 minutes. The peak height was used with the internal standard peak height to form a ratio for calculating the amount of DCPD/Codimer Concentrate in the samples. Representative GC chromatograms are shown in Appendix C, Figures 2(a - d). The test substance was not detected in the 0 mg/mL control.

B. Recovery Samples
(Appendix C)

Detailed analytical results of recovery samples are summarized in Appendix C, Table I. The measured concentrations of DCPD/Codimer Concentrate in the recovery samples for the 2.5 mg/mL level were 94.4% and 110.5% of nominal (mean percent recovery = 100.8% ± 8.5, C.V. = 8%). The measured concentrations of DCPD/Codimer Concentrate for the 12.5 mg/mL level were 92.3% and 101.6% of nominal (mean percent recovery = 98.0% ± 5.0, C.V. = 5%). The measured concentrations of DCPD/Codimer Concentrate for the 50 mg/mL level were 94.5% and 104.1% of nominal (mean percent recovery = 98.1% ± 5.3, C.V. = 5%). Based on these data, the analytical method performed satisfactorily for all dose levels in the study.

C. Homogeneity/Concentration Verification and Stability Samples

Analytical results from dosing formulations collected on April 10, 2003 and analyzed for homogeneity/concentration verification and stability are shown in Appendix C, Table II and Summary Table 1.

The following table summarizes the results for all homogeneity/concentration verification and stability analyses.

Preparation Day Sample Type	Nominal mg/mL	Measured T,M,B[a] mg/mL	Mean (T,M,B) % Nominal	C.V. (%)	Stability[b] % Nominal
10-Apr-03 Homogeneity	0	ND[c]	---	---	---
	2.50	2.70, 2.53, 2.51	103.2	4	100.0
	12.5	13.1, 12.5, 12.1	100.5	4	98.4
	50.0	49.1, 47.6, 48.4	96.8	2	101.0

a Mean results for the analysis of the top (T), middle (M), and bottom (B) samples.
b Samples held 5 hours at room temperature.
c Denotes none detected.

The data for samples collected on April 10, 2003 indicate that the test substance was homogeneously mixed in the vehicle at all levels (C.V.'s = 4, 4, and 2, respectively). The test substance was at the targeted concentration in the samples (± 3.2% of nominal) and was stable in the vehicle when held 5 hours at room temperature.

Test substance was not found in the 0 mg/mL samples.

D. Concentration Verification Samples

Analytical results from dosing formulations prepared April 21, 2003 and May 15, 2003 and analyzed for concentration verification are shown in Appendix C, Table III and Summary Table 1.

The following table summarizes the results for concentration verification analyses of the DCPD/Codimer Concentrate sample preparations.

Preparation Day	Nominal mg/mL	Measured[a] mg/mL	Average % Nominal	CV %
21-Apr-2003	0	ND[b]	---	---
	2.50	2.77, 2.73	110.0	1
	12.5	13.5, 12.6	104.4	5
	50.0	52.9,[c] 52.0	104.9	1
15-May-2003	0	ND[b]	---	---
	2.50	2.61, 2.52	102.6	2
	12.5	13.0, 12.4	101.6	3
	50.0	48.7, 48.2	96.9	1

a Duplicate samples per level were analyzed. C.V. calculated to verify uniformity of mixture.
b Denotes none detected.
c Mean result of duplicate reanalysis of the original sample #1. Original result is not reported due to aliquot error for the analysis.

The data for samples collected on April 21, 2003 indicate that the test substance was uniformly mixed in the vehicle at all levels (C.V.'s = 1, 5, and 1, respectively) and that the test substance was at the targeted concentration (± 10.0% of nominal).

The data for samples collected on May 15, 2003 indicate that the test substance was uniformly mixed in the vehicle at all levels (C.V.'s = 2, 3, and 1, respectively) and that the test substance was at the targeted concentration (± 3.1% of nominal).

Test substance was not found in the 0 mg/mL samples.

E. Analytical Evaluation Conclusions

Data from the analysis of the samples at the start of the study indicate that the test substance was mixed homogeneously, was at the targeted levels, and stable under the conditions of the study. The data for the concentration verification indicated that the test substance was mixed uniformly in the vehicle and at the targeted concentration during the study. Test substance was not found in the 0 mg/mL samples.

F. Test Substance Stability Analyses (Appendices D-E)

Samples of the test substance were analyzed near the beginning and end of the study. These analyses indicated that the DCPD/Codimer Concentrate was stable over the course of the study.

The average of the DCPD/Codimer Concentrate component (based on DCPD isomer #2) was 25.2% ± 0.50 and 24.7% ± 0.85 for samples analyzed on February 19, 2003 and May 14, 2003. This work is reported in analytical reports HA-2003-026[(2)] and Dupont-13129.[(3)] The DCPD/Codimer isomer #2 was reported by Haskell Laboratory characterization analysis to be

28.6%. The difference between the Haskell Laboratory reported characterization analysis and the experimental data represents analytical variability.

In-Life Toxicology

A. Clinical Observations and Mortality in Subchronic Males and Females

1. Subchronic Males
(Tables 2-4, Appendices F-G)

There were no test substance-related or statistically significant differences in the incidences of predosing, postdosing, or detailed clinical observations for males administered any dosage of the test substance. Unscheduled mortality did not occur during the study.

2. Subchronic Females
(Tables 5-7, Appendices H-I)

There were no test substance-related or statistically significant differences in the incidences of predosing, postdosing, or detailed clinical observations for subchronic females administered any dosage of the test substance. Unscheduled mortality did not occur during the study.

B. Body Weight and Body Weight Gain in Subchronic Males and Females

1. Subchronic Males
(Tables 8-9, Appendix J)

There were no test substance-related or statistically significant differences in body weight or weight gain for males administered any dosage of the test substance.

2. Subchronic Females
(Tables 10-11, Appendix K)

Females administered 100 mg/kg/day had significantly decreased weight gain during test days 1-8, 22-29, and over the interval of test days 1-29 (decreased 35%, 43%, and 22%, respectively, compared to control). Females administered 25 mg/kg/day also had decreased weight gain for test days 1-8, test days 22-29 (statistically significant), and over the interval of test days 1-29 (decreased 34.5%, 44%, and 13%, respectively, compared to control). However, mean body weights on day 29 for females administered 25 or 100 mg/kg/day were only 3% and 4% lower than the control value, respectively. In addition, there were no test substance-related effects on body weight or weight gain for satellite females during premating, gestation, or lactation. Therefore, the decreased weight gain in 25 and 100 mg/kg/day females was not considered to be biologically adverse since the reduction in body weight on test day 29 was less than 5% of the control value and since similar changes were not observed for satellite females.

C. Food Consumption and Food Efficiency in Subchronic Males and Females

1. Males During Premating
(Tables 12-13, Appendix L)

There were no test substance-related or statistically significant differences for food consumption or food efficiency in males administered any dosage of the test substance.

2. Subchronic Females
(Tables 14-15, Appendix M)

There were no test substance-related or statistically significant differences in food consumption or food efficiency in females administered any dosage of the test substance. Food efficiency was lower in 25 and 100 mg/kg/day females during test days 1-8, 22-29, and over the interval of test days 1-29; however, the differences were not statistically significant, and were secondary to the reduced body weight gain during these test days.

D. Clinical Signs and Mortality in Satellite Females
(Tables 16-21, Appendices N-P)

There were no statistically significant differences in the incidences of predosing or postdosing clinical observations in satellite females during premating, gestation, or lactation for any dosage. Salivation was observed in 1 female in the 100 mg/kg/day group during the predosing observation period for gestation. In addition, salivation was observed following the daily dose administration in one 100 mg/kg/day rat during gestation days 5-8. Since salivation was observed at higher dosages in the range-finding study,[(1)] it was considered to be test substance-related. However, since this was a transient observation in 1 animal, it was not considered to be adverse. Unscheduled mortality did not occur in satellite females during the study.

E. Mean Body Weights and Body Weight Gains in Satellite Females
(Tables 22-27, Appendices Q- T)

There were no test substance-related effects on body weight or weight gain for satellite females during premating, gestation, or lactation for any dosage of the test substance. Body weight gain was significantly greater in 25 mg/kg/day satellite females during gestation days 0-7. Since there were no effects at 100 mg/kg/day or during other time periods, this statistical difference was not considered to be test substance-related.

F. Mean Food Consumption and Food Efficiency in Satellite Females
(Tables 28-33, Appendices U-W)

There were no test substance-related effects on food consumption or food efficiency for satellite females administered any dosage of the test substance during premating, gestation, or lactation.

Food efficiency for 25 mg/kg/day satellite females was significantly increased compared to the control values during days 0-7 of gestation; however, this difference was not considered to be test substance-related since food efficiency was similar to the control value in 100 mg/kg/day satellite females.

G. Reproductive Indices
(Table 34, Appendices X-Y)

No test substance-related effects or statistically significant trends in mating index, fertility index, gestation length, number of implantation sites, implantation efficiency, pre-implantation loss, post-implantation loss, or number of *corpora lutea* were observed for any dosage of the test substance.

H. Offspring Data

1. Clinical Observations in Offspring
(Table 35, Appendix Z)

No test substance-related effects or statistically significant trends in the incidence of clinical observations were observed in offspring from any dosage group.

2. Litter Size, Sex Ratio, and Pup Survival (Table 36, Appendix AA)

No test substance-related effects or statistically significant trends were observed on the number of pups born, number of pups born alive, sex ratio, gestation index, or litter survival for postnatal days 0-4 in the offspring from any dosage group.

3. Pup Weights (Table 37, Appendix BB)

There were no test substance-related or statistically significant differences in pup weights on postnatal days 0, 1, or 4 for any dosage group.

I. Neurobehavioral Observations in Males and Subchronic Females

1. Grip Strength, Foot Splay, Rearing, and Body Temperature
(Tables 38-39, Figures 1-6, Appendix CC)

No test substance-related effects were observed in forelimb grip strength, hindlimb grip strength, footsplay, body temperature, or rearing during the week 4 evaluations in either males or subchronic females administered any dosage of DCPD/Codimer Concentrate.

2. Functional Observational Battery (Tables 40-41, Appendix DD)

No test substance-related or statistically significant differences in any of the 38 FOB parameters were observed during the week 4 evaluations in either males or subchronic females administered any dosage of DCPD/Codimer Concentrate.

3. Motor Activity (Tables 42-45, Figures 7-10, Appendices EE-FF)

No test substance-related or statistically significant differences in duration of movement or number of movements were observed during the baseline or week 4 evaluations in either males or subchronic females administered any dosage of DCPD/Codimer Concentrate.

J. In-Life Conclusions

Under the conditions of the study, there were no adverse test substance-related effects on mortality, clinical signs of toxicity, body weight, food consumption, reproductive parameters, neurobehavioral parameters, or offspring parameters for any dosage. The no-observed-adverse effect level was 100 mg/kg/day based on the absense of effects at 100 mg/kg/day, the highest dosage tested.

Clinical Pathology Evaluation

A. Hematology

(Tables 46-47, Appendix HH)

There were no adverse changes in hematologic parameters in male or female rats. The following statistically significant changes in mean hematologic parameters were not adverse or not related to exposure to the test substance:

- Mean cell volume and mean cell hemoglobin were minimally decreased in females dosed with 25 or 100 mg/kg/day at test day 31. There were no changes in red cell mass (red cell count, hemoglobin, hematocrit), and there were no morphologic correlates observed during the microscopic review of the blood smear. For mean cell volume, these changes were due primarily to 3 rats with unusually high mean cell volumes (2 rats in the control group and 1 rat in the 5 mg/kg/day group). For mean cell hemoglobin, the changes were due primarily to the presence of 2 rats with unusually high values (1 rat each in the control and 5 mg/kg/day groups). Therefore, these changes are unlikely to be related to treatment. Regardless, the changes are very minimal, and thus were considered to be non-adverse.

- Basophils were minimally decreased in females exposed to 5, 25, or 100 mg/kg/day at test day 31. There was no dose-relationship to the response despite the 20-fold difference in dose. Therefore, these changes were considered to be unrelated to treatment.

- Monocytes were increased in males dosed with 5 mg/kg/day at test day 30. Because there was no dose-relationship to this change, it was considered to be unrelated to treatment.

B. Coagulation
(Tables 48-49, Appendix HH)

There were no statistically significant or treatment-related changes in coagulation parameters in male or female rats.

C. Clinical Chemistry
(Tables 50-51, Appendix HH)

There were no adverse changes in clinical chemistry parameters in male or female rats. The following statistically significant changes in mean clinical chemistry parameters were not adverse or not related to exposure to the test substance:

- Bilirubin was minimally decreased in males and females dosed with 100 mg/kg/day at test days 30 and 31, respectively. In males and females, there was histologic evidence of enzyme induction (centrilobular hypertrophy), and liver weights were increased. Decreased bilirubin was likely to be secondary to enzyme induction, as a result of a physiologic response to dosing of a xenobiotic. Therefore, these changes were considered to be non-adverse.

- Calcium was minimally decreased in males dosed with 100 mg/kg/day at test day 30. However, the range of calcium concentrations in individual animals was similar across dose groups. This change, although not likely related to treatment, was considered to be non-adverse because the change was very small and within the normal variability of the parameter on this study.

The following statistically significant changes in mean clinical chemistry parameters were considered to be unrelated to treatment and non-adverse because they did not occur in a dose-related pattern:

- Decreased albumin in males dosed with 5 mg/kg/day at test day 30.

- Decreased alkaline phosphatase in females dosed with 25 mg/kg/day at test day 31.

- Increased total protein in females dosed with 25 mg/kg/day at test day 31.

D. Clinical Pathology Conclusions

In conclusion, dosing of 100 mg/kg/day resulted in minimally decreased bilirubin in males and female rats. This change was considered to be non-adverse. Therefore, under the conditions of this study and for the clinical pathology parameters measured, the no-adverse-effect level was 100 mg/kg/day for males and females, based on the lack of adverse effects at any dose.

Anatomic Pathology Evaluation for Subchronic Rats

A. Mortality

There were no test substance-related deaths. All 96 rats survived until the scheduled sacrifice date.

B. Organ Weights

(Tables 52-53, Appendix II)

In the subchronic toxicity study, test substance-related organ weight increases were observed in the kidneys of male rats and the liver of male and female rats.

Test Substance-Related Effects on Absolute and Relative Organ Weights In Male and Female Rats

	Male				Female			
Dose (mg/kg/day):	0	5	25	100	0	5	25	100
Kidney								
absolute wt. (grams)	3.22	3.64#	3.78#	3.85#	2.00	2.05	2.03	2.08
kidney wt./body wt. x 100	0.81	0.86#	0.92#	0.96#	0.86	0.86	0.88	0.92#
kidney wt./brain wt. x 100	159	179#	185#	192#	106	106	106	109
Liver								
absolute wt. (grams)	12.10	13.2	12.9	13.5#	7.01	7.37	7.34	7.73#
liver wt./body wt. x 100	3.05	3.12	3.14	3.35#	3.01	3.07	3.17	3.40#
liver wt./brain wt. x 100	597	652	628	671#	374	380	385	408#

\# Trend test (Jonckheere-Terpstra) significant.
- Underlined values were interpreted to be test-substance related weight effects.

1. Kidney

Kidney weight parameters were increased in all male treated groups (5, 25, and 100 mg/kg/day). The mean absolute kidney weights were increased 13%, 17%, and 20% over the control mean in the low-, intermediate-, and high-dose groups, respectively. Each of these increases was statistically significant by the trend test. In male rats, this kidney weight effect correlated with the microscopic finding of hyaline droplet accumulation in renal tubular epithelium (see Microscopic Findings). In female rats, marginal increases in kidney weight parameters in the

high-dose group, as compared to the control group, were considered to be biologically insignificant. Female rats did not have microscopic hyaline droplet accumulation.

2. Liver

Liver weight parameters were increased in the 100 mg/kg/day male and female rats. At the high-dose, mean absolute liver weights were increased 12% and 10% in males and females, respectively, as compared to controls. Each of these increases was statistically significant by the trend test. These liver weight effects corresponded to treatment-related hepatocellular hypertrophy (see Microscopic Findings).

3. Other

All other individual and mean organ weight differences were considered to be spurious and unrelated to test substance administration.

C. Gross Observations

(Tables 55-56, Appendix JJ)

Test substance-related gross observations were limited to the finding of bilateral pale discoloration of the kidney in all treated male groups. The incidence was dose-related and correlated with the microscopic finding of hyaline droplet accumulation in proximal tubular epithelial cells. All other gross observations at necropsy were interpreted to be naturally occurring background lesions that are typical of rats of this age and strain.

Test Substance-Related Effects on the Incidence of Gross Observations In Male and Female Rats

	Male				Female			
Dose (mg/kg/day):	0	5	25	100	0	5	25	100
Number of Rats:	12	12	12	12	12	12	12	12
Kidney								
Discoloration, pale, bilateral	0	1	5	8	0	0	0	0

- Underlined values were interpreted to be test-substance related increases in gross observations.

D. Microscopic Findings

(Tables 58-59, Appendix JJ)

Test substance-related microscopic findings were present in the kidney of male rats and the liver and thyroid of male and female rats.

Test Substance-Related Effects on the Incidence of Microscopic Findings In Male and Female Rats

	Male				Female			
Dose (mg/kg/day):	0	5	25	100	0	5	25	100
Number of Rats:	12	12	12	12	12	12	12	12
Kidney								
Hyaline droplets, increased	0	12	12	12	0	0	0	0
Liver								
Hypertrophy, hepatocyte, centrilobular	0	0	0	10	0	0	1	12
Thyroid Gland								
Hypertrophy, follicular cell	2	2	5	7	0	0	2	9

- Underlined values were interpreted to be test-substance related increases in microscopic findings.

1. Kidney

An increase in hyaline droplets within the epithelium of the proximal convoluted tubule (PCT) of kidneys was observed in all male rats exposed to the test substance. The increase in PCT hyaline droplets was graded as minimal to moderate and was dose-related. In the 100 mg/kg/day males, all cases were graded as moderate; in the 25 mg/kg/day males (12 rats), 6 and 6 cases were graded as mild and moderate, respectively; in the 5 mg/kg/day males (12 rats), 6 and 6 cases were graded as minimal and mild, respectively. In this 28-day study, there were no cases graded as severe (grade 4) since the hyaline droplet accumulation did not produce renal tubular cell degeneration and necrosis (i.e., hyaline droplet nephropathy). The increase in hyaline droplets observed in the study was not considered adverse.

Small quantities of hyaline droplets are a normal finding in the cytoplasm of the renal proximal convoluted tubular epithelium in male rats. Hyaline droplets consist of phagolysosomes containing the poorly hydrolysable low molecular weight protein, $\alpha_{2\mu}$ globulin. Normally, approximately 50 mg of this globulin are produced daily in the male rat liver and passed into the glomerular filtrate. More than half of the globulin is reabsorbed by the lining cells of the PCT. Several xenobiotics, including unleaded gasoline and d-limonene, increase the accumulation of hyaline droplets in the PCT by binding to the $\alpha_{2\mu}$ globulin. Excessive accumulation of these hyaline droplets leads to a nephropathy characterized by degeneration and necrosis of tubular epithelium, increased chronic progressive nephropathy with secondary epithelial proliferation, and, potentially following long-term exposure, neoplasia. Since female rats, and most other species including mice, dogs, monkeys and humans, do not produce significant quantities of the $\alpha_{2\mu}$ globulin, experimental findings related to hyaline droplet accumulation in male rats are not relevant to other species.[32]

The hyaline droplet accumulation in males correlated with the increased kidney weight parameters in all treated groups.[32]

2. Liver

In the liver, hypertrophy of centrilobular hepatocytes was observed in all high-dose (100 mg/kg/day) females and most (10/12) high-dose males and was graded minimal or mild (grades 1 or 2). In the 25 mg/kg/day females, 1 of 12 rats had hypertrophy and was graded as minimal. Microscopically, hepatocellular hypertrophy was characterized by an increased amount of finely granular eosinophilic cytoplasm within centrilobular hepatocytes. There was no histomorphologic evidence of hepatocellular damage, and hepatic enzyme levels were not elevated (see Clinical Pathology section). Thus, hepatocellular hypertrophy (and the associated increase in liver weights) was considered a test substance-related pharmacological response to the metabolism of a xenobiotic and not adverse.

3. Thyroid

An increased incidence of thyroid follicular cell hypertrophy was present in male and female rats given 25 and 100 mg/kg/day. All cases were graded minimal or mild. Follicular cell hypertrophy was characterized by low columnar follicular epithelium with a finely granular or vacuolated cytoplasm. Follicles were decreased in size, irregular in shape, and contained decreased amounts of normal pink colloid. The presence of minimal hypertrophy in 2 of 12 male control rats demonstrated the background incidence of this physiological change in males. Although only 2 of 12 female rats given 25 mg/kg/day had hypertrophy, these were considered treatment-related because of the lower background incidence in females.

An increase in the incidence and severity of thyroid follicular cell hypertrophy is indicative of altered thyroid gland homeostasis. Although the follicular cell response observed in this study (minimal to mild hypertrophy) was within the range of normal physiological response, the effect is potentially proliferative and adverse, especially in the rat. Since follicular cell hypertrophy is consistent with several different mechanisms of altered thyroid gland homeostasis, the specific cause of the hypertrophic response in this study is not clear. In rats, a common cause of thyroid follicular cell hypertrophy is an increase in the rate of hepatic thyroxine (T_4) glucuronidation and subsequent biliary excretion.[33] An increased rate of T_4 excretion results in lower T_4 blood levels which triggers an increase in the release of pituitary-derived thyroid stimulating hormone (TSH), resulting in thyroid follicular cell hypertrophy. Many inducers of hepatic cytochrome P450 isoenzymes in the rat are known to secondarily cause thyroid follicular cell hypertrophy by this mechanism. In this study, the presence of test substance-related hepatocellular hypertrophy in the males and females demonstrates that hepatocellular enzyme systems have been induced and that T_4 excretion may have been secondarily increased. Due to differences in T_4 half-life, thyroglobulin binding, and the ease of UDP-glucuronyl-transferase induction, rats are much more susceptible than humans to secondary thyroid follicular cell hypertrophy.[33]

4. Other

All other microscopic observations in this study are known to occur naturally in rats of this strain and age and were not present in a dose-response fashion in either incidence or severity.

E. Anatomic Pathology Conclusions

Exposure to 5, 25, and 100 mg/kg/day of the test substance for approximately 28 days produced a dose-related increase in renal tubular hyaline droplets in male rats with associated increases in kidney weight parameters. Hyaline droplet nephropathy was not observed. Increased hyaline droplets were not observed in females. Minimal to mild hepatocellular hypertrophy was observed in males and females given 100 mg/kg/day and in 1 female given 25 mg/kg/day. An associated increase in liver weight parameters was observed in both sexes at the highest dose. Minimal to mild thyroid follicular hypertrophy occurred in males and females given 25 and 100 mg/kg/day.

The hyaline droplet accumulation in male rats was not an adverse effect in these animals and is considered species and sex specific and not predictive of an effect in other species. The hepatocellular hypertrophy and slightly increased liver weights in both sexes was consistent with enzyme induction as a pharmacological response to a xenobiotic and was not considered to be adverse. The thyroid effect, although mild, was regarded as potentially adverse.

Under the conditions of this study, there was no NOEL for pathology for male rats based on the increase in hyaline droplets in the kidney at all dose levels. The NOEL for pathology for female rats was 5 mg/kg/day, based on the finding of the potentially adverse thyroid follicular cell hypertrophy in female rats given 25 or 100 mg/kg/day.

Anatomical Pathology Evaluation for Satellite Females

A. Mortality

Parental P_1 Adults

In the P_1 adult generation, there was no test substance-related effect on mortality. There were no deaths among the 48 males (subchronic toxicity study) or 48 satellite female rats.

B. Organ Weight Data

P_1 Adults (Table 54 Appendix KK)

Data for the P_1 males is presented with the subchronic toxicity study since those males were cohabited with the P_1 female satellite groups for production of the F_1 offspring.

In the satellite P_1 females, a test substance-related organ weight increase was observed in the liver of rats given 100 mg/kg/day for approximately 28 days. At the high dose, the mean absolute liver weight was increased 16% over the control mean.

Test Substance-Related Effects on Absolute and Relative Organ Weights In P_1 Female Rats (Satellite Groups)

	Female			
Dose (mg/kg/day):	0	5	25	100
Liver				
absolute wt. (grams)	12.6	13.0	13.6	14.7#
liver wt./body wt. x 100	4.16	4.19	4.42	4.76#
liver wt./brain wt. x 100	662	637	685	781#

\# Trend test (Jonckheere-Terpstra) significant.
\- Underlined values were interpreted to be test-substance related weight effects.

C. Gross Observations

Parental P_1 Adults (Table 57, Appendix LL)

Data for the P_1 males is presented with the subchronic toxicity study.

No test substance-related gross observations were observed in the P_1 females (satellite females). All gross observations at necropsy were interpreted to be naturally occurring background lesions that are typical of rats of this age and strain.

D. Microscopic Observations

Parental P_1 Adults (Table 60, Appendix MM)

Microscopic examination of P_1 adults included examination of the reproductive organs of the 5 cohabiting pairs that failed to produce litters (i.e., reproductive failures). The affected pairs included 2 Group I/II-0 pairs (male Animal Number 671688 and female Animal Number 671776; male Animal Number 671709 and female Animal Number 671795), 1 Group V/VI-0 pair (male Animal Number 671680 and female Animal Number 671749), and 2 Group VII/VIII-0 pairs (male Animal Number 671686 and female Animal Number 671752; male Animal Number 671692 and female Animal Number 671777).

Microscopic examination of the reproductive organs of the 5 non-producing pairs revealed that 1 Group VIII-0 female rat (Animal Number 671777) had mild endometritis of the uterus with bacteria. The microscopic endometritis correlated with the gross observation of severe dilatation of the uterus and vagina with yellow fluid. This uterine infection, which was not test substance-related, would account for the infertility in this pair. There were no other gross or microscopic findings that were related to fertility in these five pairs of rats.

E. Anatomical Pathology Conclusions for Reproductive Toxicity

For pathology, the NOAEL was 100 mg/kg/day (the highest dose level) for the female satellite groups based on the finding of only a pharmacological, non-adverse, increase in liver weight parameters in the 100 mg/kg/day dose group.

The pathology results of the P_1 male rats are included in the subchronic toxicity study.

CONCLUSIONS

There were no adverse, test substance-related clinical signs of toxicity in males, subchronic females, or satellite females administered any dosage of the test substance. Unscheduled mortality did not occur at any dosage in males, subchronic females, or satellite females.

Decreased weight gain was observed in 25 and 100 mg/kg/day subchronic females. However, since body weight was only 3% and 4% lower than the control values on test day 29 in 25 and 100 mg/kg/day subchronic females, respectively; and since there were no effects on body weight gain in satellite females, the decreased body weight gain was not considered to be biologically adverse.

There were no test substance-related, statistically significant effects on food consumption or food efficiency in males, subchronic females, or satellite females administered any dosage of the test substance.

No test substance-related effects or statistically significant differences in mating index, fertility index, gestation length, number of implantation sites, implantation efficiency, pre-implantation loss, post-implantation loss, or number of *corpora lutea* were observed for any dosage of the test substance in satellite females.

There were no test substance-related effects on mean pup weight, number of pups born, number of pups born alive, sex ratio, gestation index, clinical observations, or litter survival for postnatal days 0-4 in the offspring from any dosage group.

There were no test substance-related effects observed in any neurobehavioral parameter for males or subchronic females administered any dosage of the test substance.

There were no adverse, statistically significant or treatment-related changes in hematological, coagulation, or clinical chemistry parameters in male or subchronic female rats.

Administration of 5, 25, or 100 mg/kg/day of the test substance for approximately 28 days produced a dose-related increase in renal tubular hyaline droplets in male rats which was correlated with an increase in the incidence of bilateral pale kidney discoloration, and with changes in kidney weight parameters. Increased hyaline droplets were not observed in females, although 100 mg/kg/day subchronic females had a slight increase in kidney weight parameters which was biologically insignificant. The hyaline droplet accumulation in male rats was not considered to be an adverse effect of the test substance. Also, renal tubular hyaline droplet accumulation is species and sex specific, and is not predictive of an effect in other species.

Hepatocellular hypertrophy, and associated increases in liver weight parameters were observed in 100 mg/kg/day males, subchronic females, and in satellite females. One subchronic female in the 25 mg/kg/day group also had hepatocellular hypertrophy. However, hepatocellular hypertrophy is considered to be secondary to enzyme induction as a pharmacological response to a xenobiotic, and was not considered to be adverse.

Thyroid follicular cell hypertrophy was observed in 25 and 100 mg/kg/day males and females, which was considered to be test substance-related and potentially adverse.

No morphological changes were detected in reproductive tissues for females or males administered any dosage of the test substance.

The NOEL was not determined for males based on increased incidence of renal tubular hyaline droplets at all dosages, and, therefore, the LOEL level was 5 mg/kg/day, the lowest dosage tested. However, since hyaline droplets are not considered to be relevant for humans, the NOAEL for males was 5 mg/kg/day. The NOEL and NOAEL in females was 5 mg/kg/day based on thyroid follicular cell hypertrophy at 25 mg/kg/day. The LOEL in females was, therefore, 25 mg/kg/day.

The NOEL and NOAEL for reproductive parameters was considered to be 100 mg/kg/day based on the absence of effects on mating index, fertility index, gestation length, number of implantation sites, implantation efficiency, pre-implantation loss, post-implantation loss, or number of *corpora lutea* at any dosage.

The NOEL and NOAEL for developmental toxicity was considered to be 100 mg/kg/day based on the absence of effects in offspring at any dosage.

The NOEL and NOAEL for neurobehavioral parameters was considered to be 100 mg/kg/day in males and females based on the absence of effects at any dosage.

RECORDS AND SAMPLE STORAGE

All original records will be retained at Haskell Laboratory, E.I. du Pont de Nemours and Company, Newark, Delaware, or at Iron Mountain Records Management, Wilmington, Delaware. Preserved wet tissues, paraffin blocks, histological slides, blood smears, and bone marrow smears will be retained at Haskell Laboratory.

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TABLES

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Hematology Values

RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular volume
MCH	-	mean corpuscular hemoglobin
MCHC	-	mean corpuscular hemoglobin concentration
RDW	-	red cell distribution width
ARET	-	absolute reticulocyte count
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
AEOS	-	absolute eosinophil
ABAS	-	absolute basophil
ALUC	-	absolute large unstained cell
NRBC	-	nucleated red blood cell count
NC	-	not calculated or not calculable
-	-	no data

Summary of Coagulation Values

PT	-	prothrombin time
APTT	-	activated partial thromboplastin time

TABLES

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

Summary of Clinical Chemistry Values

AST	-	aspartate aminotransferase
ALT	-	alanine aminotransferase
SDH	-	sorbitol dehydrogenase
ALKP	-	alkaline phosphatase
BILI	-	total bilirubin
BUN	-	urea nitrogen
CREA	-	creatinine
CHOL	-	cholesterol
TRIG	-	triglycerides
GLUC	-	glucose
TP	-	total protein
ALB	-	albumin
GLOB	-	globulin
CALC	-	calcium
IPHS	-	inorganic phosphorous
NA	-	sodium
K	-	potassium
CL	-	chloride

NOTES:

Summary of Hematology Values
Summary of Coagulation Values
Summary of Clinical Chemistry Values
Summary of Urinalysis Values
When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that data.

TABLE 1

SUMMARY OF DOSING MIXING AND STABILITY ANALYSES

	Dosing Concentration of DCPD/Codimer Concentrate (mg/mL)		
Nominal:	**2.5**	**12.5**	**50**
Homogeneity Samples 10-Apr-2003			
Top	2.70 (108.0) [a]	13.1 (104.8)	49.1 (98.2)
Middle	2.53 (101.2)	12.5 (100.0)	47.6 (95.2)
Bottom	2.51 (100.4)	12.1 (96.8)	48.4 (96.8)
Average Measured Conc. [b]	**2.58**	**12.6**	**48.4**
Average Percent Nominal	**(103.2)**	**(100.5)**	**(96.8)**
Standard Deviation [b]	**± 0.10**	**± 0.50**	**± 0.75**
Coefficient of Variation [b]	**4%**	**4%**	**2%**
Stability Samples 5 Hour Room Temperature	2.50 (100.0)	12.3 (98.4)	50.5 (101.0)
Concentration Verification 21-Apr-2003			
#1	2.77 (110.8)	13.5 (108.0)	52.9 [c] (105.8)
#2	2.73 (108.2)	12.6 (100.8)	52.0 (104.0)
Average Measured Conc. [d]	**2.75**	**13.1**	**52.5**
Average Percent Nominal	**(110.0)**	**(104.4)**	**(104.9)**
Standard Deviation [d]	**± 0.03**	**± 0.64**	**± 0.64**
Coefficient of Variation [d]	**1%**	**5%**	**1%**
Concentration Verification 15-May-2003			
#1	2.61 (104.4)	13.0 (104.0)	48.7 (97.4)
#2	2.52 (100.8)	12.4 (99.2)	48.2 (96.4)
Average Measured Conc. [d]	**2.57**	**12.7**	**48.5**
Average Percent Nominal	**(102.6)**	**(101.6)**	**(96.9)**
Standard Deviation [d]	**± 0.06**	**± 0.42**	**± 0.35**
Coefficient of Variation [d]	**2%**	**3%**	**1%**

a Numbers in parentheses are the respective percent of nominal values.
b Statistics based on the average measured concentration (mg/mL) of the top, middle, and bottom of each dosing level.
c Mean result of duplicate reanalysis of sample #1 of the dosing level. Original analysis was not reported due to aliquot error for the analysis.
d Statistics based on the average measured concentration (mg/mL) of duplicate samples of each dosing level.

TABLE 2

SUMMARY OF CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	I	III	V	VII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
OBSERVATION				
ALOPECIA	4	3	2	4
SORE	1	0	0	0

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 3

SUMMARY OF CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	I	III	V	VII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
OBSERVATION				
COLORED DISCHARGE RIGHT EYE(S)	0	0	0	1

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 4

SUMMARY OF DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	I	III	V	VII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
PRETEST OBSERVATIONS				
ALOPECIA	2	1	0	0
DOSING PERIOD OBSERVATIONS				
ALOPECIA	4	3	2	4
SORE	1	0	0	0

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 5

SUMMARY OF CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II	IV	VI	VIII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
OBSERVATION				
ALOPECIA	4	4	3	3
SORE	0	0	1	0
EAR SHAKE	0	0	0	1

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 6

SUMMARY OF CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II	IV	VI	VIII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
OBSERVATION				
NO ABNORMALITIES DETECTED	12	12	12	12

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 7

SUMMARY OF DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II	IV	VI	VIII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
PRETEST OBSERVATIONS				
ALOPECIA	0	1	0	0
DOSING PERIOD OBSERVATIONS				
ALOPECIA	4	4	3	3
SORE	0	0	1	0

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 8

MEAN BODY WEIGHTS (grams) OF SUBCHRONIC MALE RATS

	MEAN BODY WEIGHTS (g)			
GROUP:	I	III	V	VII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1	264.6(9.6)	269.0(10.9)	263.2(8.5)	263.0(12.1)
8	313.4(10.3)	327.3(16.3)	315.5(15.8)	317.7(15.2)
15	357.1(14.6)	375.7(21.7)	364.9(16.7)	362.0(18.9)
22	392.2(20.3)	413.1(23.4)	403.4(21.8)	400.9(19.9)
29	424.1(25.1)	455.1(28.4)	442.4(23.3)	436.4(25.0)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

TABLE 9

MEAN BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

	MEAN BODY WEIGHT GAINS (g)			
GROUP:	I	III	V	VII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1-8	48.8(5.6)	58.3(6.7)	52.3(11.2)	54.7(7.3)
8-15	43.6(6.7)	48.4(7.6)	49.4(8.5)	44.4(5.0)
15-22	35.2(10.3)	37.4(7.2)	38.5(6.0)	38.9(5.4)
22-29	31.9(8.7)	42.1(7.7)	39.0(6.3)	35.5(7.1)
1-29	159.5(23.0)	186.2(20.0)	179.2(17.5)	173.4(20.3)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

TABLE 10

MEAN BODY WEIGHTS (grams) OF SUBCHRONIC FEMALE RATS

	MEAN BODY WEIGHTS (g)			
GROUP:	II	IV	VI	VIII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1	189.9(8.8)	192.7(11.6)	191.4(10.2)	192.8(8.5)
8	206.4(13.0)	207.3(15.8)	202.2(12.0)	203.6(14.2)
15	224.4(14.8)	223.9(14.1)	220.7(16.3)	216.9(13.9)
22	234.1(15.0)	239.7(18.4)	235.2(22.4)	231.1(14.3)
29	251.4(17.0)	254.0(24.6)	244.8(20.5)	241.1(16.2)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

TABLE 11

MEAN BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

	MEAN BODY WEIGHT GAINS (g)			
GROUP:	II	IV	VI	VIII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1-8	16.5(8.9)	14.6(8.9)	10.8(6.4)	10.7(9.2)*
8-15	17.9(10.7)	16.6(7.6)	18.5(8.7)	13.4(8.0)
15-22	9.7(8.9)	15.9(9.3)	14.4(7.3)	14.2(6.8)
22-29	17.3(8.9)	14.2(11.4)	9.7(7.3)*	9.9(7.6)*
1-29	61.5(13.5)	61.3(16.9)	53.4(14.5)	48.2(13.1)*

Data summarized as Mean (Standard Deviation)

* Statistically significant trend at p<0.05 by Jonckheere-Terpstra test.

TABLE 12

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SUBCHRONIC MALE RATS DURING PREMATING

	MEAN DAILY FOOD CONSUMED PER RAT (g)			
GROUP:	I	III	V	VII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1-8	25.9(1.3)	28.1(1.6)	25.9(3.8)	26.3(1.9)
8-15	28.1(3.8)	29.3(1.5)	28.3(2.1)	28.5(1.9)
1-15	27.0(2.3)	28.7(1.4)	27.1(2.8)	27.4(1.8)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

TABLE 13

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SUBCHRONIC MALE RATS DURING PREMATING

	MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)			
GROUP:	I	III	V	VII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1-8	0.269(.027)	0.296(.029)	0.285(.040)	0.297(.034)
8-15	0.223(.034)	0.235(.029)	0.251(.048)	0.222(.022)
1-15	0.245(.025)	0.265(.023)	0.269(.029)	0.258(.024)

Data summarized as Mean (Standard Deviation)

There were no statistically significant differences at $p<0.05$ by One-Way Analysis of Variance and Dunnett's test.

TABLE 14

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SUBCHRONIC FEMALE RATS

	MEAN DAILY FOOD CONSUMED PER RAT (g)			
GROUP:	II	IV	VI	VIII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1-8	19.6(1.2)[a]	19.0(2.2)	17.9(2.2)	19.1(2.1)
8-15	18.2(2.6)	18.6(1.5)	18.4(1.9)	19.0(1.9)
15-22	18.7(4.0)	18.7(2.2)	18.0(2.4)	17.8(2.0)
22-29	19.7(2.0)	19.5(2.2)	18.5(2.4)	18.5(1.8)
1-29	19.1(1.6)[a]	19.0(1.8)	18.2(2.0)	18.6(1.6)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

a N = 11. Due to technical error, food consumption was not measured for 1 animal during test days 1-8. As a result, food consumption over the interval of test days 1-29 also could not be calculated for this animal.

TABLE 15

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SUBCHRONIC FEMALE RATS

	MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)			
GROUP:	II	IV	VI	VIII
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1- 8	0.119(.060)[a]	0.109(.066)	0.085(.051)	0.075(.058)
8-15	0.137(.078)	0.127(.056)	0.140(.056)	0.100(.055)
15-22	0.067(.069)	0.118(.058)	0.112(.053)	0.111(.050)
22-29	0.125(.059)	0.098(.076)	0.075(.059)	0.077(.057)
1-29	0.115(.022)[a]	0.114(.025)	0.104(.023)	0.092(.021)

Data summarized as Mean (Standard Deviation)

There were no statistically significant differences at $p<0.05$ by One-Way Analysis of Variance and Dunnett's test.

a N = 11. Due to technical error, food consumption was not measured for 1 animal during test days 1-8. As a result, food consumption over the interval of test days 1-29 also could not be calculated for this animal.

TABLE 16

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING PREMATING (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
OBSERVATION				
ALOPECIA	0	2	2	2
SCAB	0	0	1	0

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 17

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING PREMATING (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
OBSERVATION				
COLORED DISCHARGE LEFT EYE(S)	0	0	0	1

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 18

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
OBSERVATION				
ALOPECIA	2	4	5	3
COLORED DISCHARGE LEFT EYE(S)	0	0	0	1
SALIVATION	0	0	0	1
SCAB	0	0	1	0
SORE	0	0	0	1

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

This table contains data from females that had a sperm positive lavage sample or a vaginal plug.

TABLE 19

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
OBSERVATION				
SALIVATION	0	0	0	1
SORE	0	0	0	1

There were no statistically significant trends by Cochran-Armitage test; p < 0.05.
This table contains data from females that had a sperm positive lavage sample or a vaginal plug.

TABLE 20

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
OBSERVATION				
ALOPECIA	2	4	5	2
SORE	0	0	0	1

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 21

SUMMARY OF CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

	NUMBER OF RATS WITH GIVEN SIGN			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
OBSERVATION				
No Abnormalities Detected	10	12	11	10

There were no statistically significant trends by Cochran-Armitage test; $p < 0.05$.

TABLE 22

MEAN BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING PREMATING

	MEAN BODY WEIGHTS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1	191.5(7.6)	195.2(7.6)	192.6(8.8)	192.8(12.0)
8	206.4(7.9)	210.0(6.5)	205.8(9.3)	208.3(14.2)
15	224.4(9.6)	226.3(8.2)	226.3(17.4)	228.4(12.8)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

TABLE 23

MEAN BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING PREMATING

	MEAN BODY WEIGHT GAINS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1- 8	14.9(5.1)	14.8(7.0)	13.2(5.3)	15.5(8.2)
8-15	18.0(5.0)	16.4(6.3)	20.5(10.8)	20.1(9.5)
1-15	32.9(8.4)	31.1(8.0)	33.7(11.4)	35.6(8.0)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

TABLE 24

MEAN BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

	MEAN BODY WEIGHTS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
GESTATION DAYS				
0	232.6(11.8)	241.7(16.8)	232.0(15.1)	233.2(15.4)
7	269.9(10.7)	282.5(15.2)	280.3(15.3)	278.0(18.0)
14	308.0(10.4)	324.0(17.5)	319.3(14.8)	314.4(21.4)
21	397.1(13.9)	414.1(21.1)	400.3(25.8)	397.1(23.8)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

This table contains data from females that had a sperm positive lavage sample or a vaginal plug.

TABLE 25

MEAN BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING GESTATION

	MEAN BODY WEIGHT GAINS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
GESTATION DAYS				
0-7	37.2(8.0)	40.8(8.0)	48.3(7.0)*	44.8(6.6)
7-14	38.1(6.2)	41.5(5.3)	39.0(9.1)	36.4(8.1)
14-21	89.2(10.9)	90.2(9.7)	81.0(23.7)	82.7(12.1)
0-21	164.5(9.7)	172.4(14.3)	168.3(27.6)	163.9(16.5)

Data summarized as Mean (Standard Deviation)

* Statistically significant trend at p<0.05 by Jonckheere-Terpstra test.

This table contains data from females that had a sperm positive lavage sample or a vaginal plug.

TABLE 26

MEAN BODY WEIGHTS (grams) OF SATELLITE FEMALE RATS DURING LACTATION

	MEAN BODY WEIGHTS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
LACTATION DAYS				
0	296.6(12.4)	303.7(19.2)	304.8(17.2)	292.6(24.5)
4	307.2(14.6)	311.0(24.4)	309.3(27.3)	309.8(24.0)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

TABLE 27

MEAN BODY WEIGHT GAINS (grams) OF SATELLITE FEMALE RATS DURING LACTATION

	MEAN BODY WEIGHT GAINS (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
LACTATION DAYS				
0-4	10.6(7.9)	7.4(18.5)	4.5(22.9)	17.2(14.7)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

TABLE 28

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SATELLITE FEMALE RATS DURING PREMATING

	MEAN DAILY FOOD CONSUMED PER RAT (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1- 8	18.0(1.3)	18.3(2.1)	18.3(2.5)	18.0(1.7)
8-15	19.0(1.7)	18.6(1.1)	18.5(2.0)	19.2(1.5)
1-15	18.5(1.0)	18.5(1.4)	18.4(2.1)	18.6(1.3)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

TABLE 29

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SATELLITE FEMALE RATS DURING PREMATING

	MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	12	12	12	12
DAYS ON TEST				
1- 8	0.119(.040)	0.115(.056)	0.103(.040)	0.121(.061)
8-15	0.136(.041)	0.126(.052)	0.154(.073)	0.149(.070)
1-15	0.127(.032)	0.120(.030)	0.129(.033)	0.137(.030)

Data summarized as Mean (Standard Deviation)

There were no statistically significant differences at $p<0.05$ by One-Way Analysis of Variance and Dunnett's test.

TABLE 30

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SATELLITE FEMALE RATS DURING GESTATION

	MEAN DAILY FOOD CONSUMED PER RAT (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
GESTATION DAYS				
0-7	23.9(1.8)	24.5(3.5)	23.6(1.5)	24.2(2.2)
7-14	25.9(2.8)	27.1(3.4)	25.8(2.2)	27.0(3.0)
14-21	26.8(2.3)	27.1(2.5)	26.8(2.8)	26.2(2.3)
0-21	25.5(2.0)	26.2(2.9)	25.4(1.9)	25.8(2.0)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at $p<0.05$ by Jonckheere-Terpstra test.

This table contains data from females that had a sperm positive lavage sample or a vaginal plug.

TABLE 31

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SATELLITE FEMALE RATS DURING GESTATION

	MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
GESTATION DAYS				
0-7	0.225(.057)	0.240(.043)	0.292(.039)*	0.266(.036)
7-14	0.211(.032)	0.221(.033)	0.216(.045)	0.192(.038)
14-21	0.476(.054)	0.477(.047)	0.429(.110)	0.452(.058)
0-21	0.308(.027)	0.315(.029)	0.315(.044)	0.304(.033)

Data summarized as Mean (Standard Deviation)

* Statistically significant at $p<0.05$ by One-Way Analysis of Variance and Dunnett's test.

This table contains data from females that had a sperm positive lavage sample or a vaginal plug.

TABLE 32

MEAN DAILY FOOD CONSUMPTION (grams/day) OF SATELLITE FEMALE RATS DURING LACTATION

	MEAN DAILY FOOD CONSUMED PER RAT (g)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
LACTATION DAYS				
0-4	34.6(4.8)	30.5(7.7)	30.8(7.1)	33.6(5.9)

Data summarized as Mean (Standard Deviation)

There were no statistically significant trends at p<0.05 by Jonckheere-Terpstra test.

TABLE 33

MEAN FOOD EFFICIENCY (grams weight gained/grams food consumed) OF SATELLITE FEMALE RATS DURING LACTATION

	MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)			
GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
LACTATION DAYS				
0-4	0.073(0.058)	0.025(0.175)	0.015(0.244)	0.144(0.160)

Data summarized as Mean (Standard Deviation)

There were no statistically significant differences at $p<0.05$ by One-Way Analysis of Variance and Dunnett's test.

TABLE 34

SUMMARY OF REPRODUCTIVE INDICES: P_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
MATING INDEX (%)[a]	83.3	100.0	100.0	100.0
(# copulated/cohoused)	(10/12)	(12/12)	(12/12)	(12/12)
FERTILITY INDEX (%)[b]	100.0	100.0	91.7	83.3
(# delivered/copulated)	(10/10)	(12/12)	(11/12)	(10/12)
GESTATION LENGTH (days)[c]	22.1	22.2	22.1	22.0
(# in group)	(10)	(12)	(11)	(10)
NUMBER OF IMPLANTATION SITES				
per pregnant female	15.0	16.5	13.4	15.3
Standard deviation (# in group)	2.2(10)	1.4(12)	4.8(11)	1.8(10)
IMPLANTATION EFFICIENCY (%)[d]	94.5	93.1	92.5	91.6
Standard deviation (# in group)	9.1(10)	4.6(12)	11.8(11)	7.7(10)
NUMBER OF CORPORA LUTEA				
per pregnant female	15.6	16.8	15.7	16.6
Standard deviation (# in group)	2.0(10)	1.6(12)	2.4(11)	2.5(10)
PRE-IMPLANTATION LOSS	0.0	0.0	0.2	0.1
Standard deviation (# in group)	0.1(10)	0.0(12)	0.2(11)	0.1(10)
POST-IMPLANTATION LOSS	0.1	0.1	0.1	0.1
Standard deviation (# in group)	0.1(10)	0.1(12)	0.2(11)	0.1(10)

a Evidence of copulation = Intravaginal copulation plug, sperm in vaginal lavage, implantations observed at necropsy, or delivery of a litter.
b Pregnant = Delivery of a litter or implantation sites at necropsy.
c Gestation length could not be calculated for those females that were pregnant for which no evidence of copulation was observed.
d Number of pups born/number of implantation sites X 100.

There were no statistically significant trends in mating or fertility indices by Cochran-Armitage test; $p < 0.05$.

There were no statistically significant trends in gestation length, number of implantation sites, implantation efficiency, number of *corpora lutea*, pre-implantation loss or post-implantation loss by Jonckheere-Terpstra test; $p<0.05$.

TABLE 35

SUMMARY OF PUP CLINICAL OBSERVATIONS: F_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
OBSERVATIONS				
TOTAL NUMBER OF SIGNS	0	0	0	0
NUMBER OF LITTERS AFFECTED	0	0	0	0

There were no statistically significant trends by Cochran-Armitage test; $p<0.05$.

TABLE 36

MEAN PUP NUMBERS AND SURVIVAL: F_1 GENERATION

MATERNAL GROUP:	II-0	IV-0	VI-0	VIII-0
DOSAGE (MG/KG/DAY):	0	5	25	100
N:	10	12	11	10
	MEAN NUMBER OF PUPS/LITTER			
Born	14.1	15.3	12.5	14.0
Born Alive	13.9	15.1	12.5	13.9
Day 1	13.6	15.0	12.5	13.8
Day 4	13.6	14.8	12.5	13.6
	MEAN NUMBER OF MALE PUPS/LITTER			
Born	7.5	7.8	6.2	7.0
Born Alive	7.5	7.6	6.2	7.0
Day 1	7.4	7.5	6.1	7.0
Day 4	7.4	7.3	6.1	6.8
	MEAN NUMBER OF FEMALE PUPS/LITTER			
Born	6.6	7.6	6.4	7.0
Born Alive	6.4	7.5	6.4	6.9
Day 1	6.2	7.5	6.4	6.8
Day 4	6.2	7.4	6.4	6.8
Sex Ratio (males)	0.53	0.51	0.48	0.51
Gestation Index[a]	100.0	100.0	100.0	100.0
Mean % Born Alive	98.5	98.5	100.0	99.3
0-4 Day Viability	98.2	97.9	99.3	97.8

a Percent litters delivered having at least 1 live pup.

There were no statistically significant trends in number of pups, sex ratio, mean percent born alive, or 0-4 day viability by Jonckheere-Terpstra test; $p < 0.05$.

There were no statistically significant trends in gestation index by Cochran-Armitage test; $p < 0.05$.

Statistics were performed on combined pups per litter only. Male and female data are presented for information only.

TABLE 37

MEAN PUP WEIGHTS: F_1 GENERATION

Maternal Group:	II-0	IV-0	VI-0	VIII-0
Dosage (mg/kg/day):	0	5	25	100
N:	10	12	11	10
		MEAN PUP WEIGHTS		
Day 0	6.5(0.3)	6.6(0.5)	6.7(0.8)	6.4(0.4)
Day 1	7.3(0.4)	7.3(0.6)	7.6(1.1)	7.0(0.5)
Day 4	10.6(0.8)	10.3(1.3)	11.0(2.2)[a]	10.2(0.8)
		MEAN MALE PUP WEIGHTS		
Day 0	6.7(0.4)	6.8(0.4)	6.8(0.7)	6.5(0.4)
Day 1	7.5(0.4)	7.5(0.5)	7.8(1.0)	7.2(0.5)
Day 4	10.8(0.9)	10.6(1.3)	11.2(2.1)[a]	10.4(0.9)
		MEAN FEMALE PUP WEIGHTS		
Day 0	6.4(0.3)	6.4(0.5)	6.5(0.9)	6.2(0.2)
Day 1	7.1(0.3)	7.1(0.5)	7.4(1.2)	6.8(0.3)
Day 4	10.4(0.7)	10.0(1.2)	10.8(2.4)[a]	10.0(0.6)

Data were summarized as Mean (Standard Deviation).

a N = 10 due to weights of pups from 1 litter that were inadvertently not recorded on lactation day 4.

There were no statistically significant trends by linear contrast of least square means; $p < 0.05$.

Statistics were performed on combined pups per litter only. Male and female data are presented for information only.

TABLE 38

MEAN FORELIMB AND HINDLIMB GRIP STRENGTH, HINDLIMB SPLAY, BODY TEMPERATURE, AND REARING FOR MALE RATS

GROUP	DOSAGE (mg/kg/day)	FORELIMB GRIP STRENGTH (kg) MEAN	(S.D.)	HINDLIMB GRIP STRENGTH (kg) MEAN	(S.D.)	HINDLIMB SPLAY (cm) MEAN	(S.D.)	BODY TEMPERATURE (ºC) MEAN	(S.D.)	REARING (Number) MEAN	(S.D.)	BODY WEIGHT (g) MEAN	(S.D.)
BASELINE													
I	0	0.62	(0.07)	0.38	(0.05)	7.2	(1.2)	35.7	(0.5)	3	(3)	208.4	(6.7)
III	5	0.62	(0.11)	0.39	(0.06)	6.9	(1.8)	35.8	(0.4)	3	(2)	208.8	(8.2)
V	25	0.61	(0.09)	0.39	(0.06)	7.9	(1.6)	35.7	(0.7)	4	(3)	208.7	(6.8)
VII	100	0.65	(0.13)	0.38	(0.05)	7.4	(1.7)	35.5	(0.6)	5	(3)	208.6	(7.5)
WEEK 4													
I	0	1.43	(0.17)	0.61	(0.08)	8.4	(2.7)	33.5	(0.4)	4	(2)	424.1	(25.1)
III	5	1.25	(0.34)	0.65	(0.10)	8.9	(1.8)	33.4	(0.3)	4	(3)	455.1	(28.4)
V	25	1.36	(0.32)	0.68	(0.11)	9.5	(1.9)	33.5	(0.4)	5	(3)	442.4	(23.3)
VII	100	1.32	(0.21)	0.59	(0.09)	9.0	(2.2)	33.4	(0.4)	4	(3)	436.4	(25.0)

N = 12 rats per group

Statistical Methods: Shapiro-Wilk test for normality and Levene's test for homogeneity were performed. Repeated measures analysis of variance with linear contrasts or Jonckheere's trend test was used to identify which groups, if any, were significantly different from the control group. These tests were applied to Interval data and Total data.

There were no statistically significant trends or differences compared to control at $p < 0.05$.

TABLE 39

MEAN FORELIMB AND HINDLIMB GRIP STRENGTH, HINDLIMB SPLAY, BODY TEMPERATURE, AND REARING FOR FEMALE RATS

GROUP	DOSAGE (mg/kg/day)	FORELIMB GRIP STRENGTH (kg) MEAN	(S.D.)	HINDLIMB GRIP STRENGTH (kg) MEAN	(S.D.)	HINDLIMB SPLAY (cm) MEAN	(S.D.)	BODY TEMPERATURE (ºC) MEAN	(S.D.)	REARING (Number) MEAN	(S.D.)	BODY WEIGHT (g) MEAN	(S.D.)
BASELINE													
II	0	0.57	(0.12)	0.36	(0.05)	6.5	(2.1)	37.0	(0.4)	6	(3)	171.7	(8.1)
IV	5	0.65	(0.16)	0.35	(0.06)	6.5	(0.9)	37.0	(0.5)	4	(2)	171.2	(10.7)
VI	25	0.62	(0.09)	0.36	(0.05)	6.2	(2.2)	37.0	(0.6)	6	(3)	175.7	(9.7)
VIII	100	0.56	(0.11)	0.32	(0.04)	6.1	(1.3)	36.7	(0.6)	7	(2)	172.0	(8.3)
WEEK 4													
II	0	1.01	(0.19)	0.53	(0.07)	6.0	(2.3)	35.2	(0.5)	9	(3)	250.4	(17.0)
IV	5	1.13	(0.19)	0.56	(0.10)	7.1	(1.9)	35.0	(0.5)	6	(2)	257.4	(23.1)
VI	25	1.06	(0.20)	0.48	(0.06)	6.2	(1.9)	35.3	(0.6)	8	(2)	246.6	(23.7)
VIII	100	1.03	(0.12)	0.52	(0.04)	6.1	(1.5)	35.3	(0.5)	10	(4)	243.3	(14.7)

N = 12 rats per group

Statistical Methods: Shapiro-Wilk test for normality and Levene's test for homogeneity were performed. Repeated measures analysis of variance with linear contrasts was used to identify which groups, if any, were significantly different from the control group. These tests were applied to Interval data and Total data.

There were no statistically significant differences from control at $p < 0.05$.

TABLE 40

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
HOME CAGE								
POSTURE								
limbs spread out or lying on one side	0	0	0	0	0	0	0	0
curled up,	2	3	1	4	4	3	2	2
sitting, standing or rearing normally, alert	10	9	11	8	8	9	10	10
jumping	0	0	0	0	0	0	0	0
PALPEBRAL CLOSURE								
eyelids wide open	11	10	11	9	11	10	11	10
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
rat appears to be sleeping	1	2	1	3	1	2	1	2
WRITHING								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
CIRCLING								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
BITING								
absent	12	12	12	12	12	12	12	12
biting others	0	0	0	0	0	0	0	0
biting cage	0	0	0	0	0	0	0	0
self mutilation	0	0	0	0	0	0	0	0
GAIT/COORDINATION								
normal	12	12	12	12	12	12	12	12
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0

TABLE 40 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
REMOVAL FROM HOME CAGE								
EASE OF REMOVAL								
too easy (rat sits quietly, no resistance)	0	0	0	0	0	0	0	0
some resistance (rears, follows observer's hand)	12	12	12	12	12	12	12	12
difficult (runs around cage, may attack)	0	0	0	0	0	0	0	0
EASE OF HANDLING								
too easy	0	0	0	0	0	0	0	0
easy (alert, limbs pulled up against body)	12	12	12	12	12	12	12	12
difficult	0	0	0	0	0	0	0	0
MUSCLE TONE								
limp	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
rigid	0	0	0	0	0	0	0	0
VOCALIZATIONS								
present	0	0	0	0	1	0	0	0
absent	12	12	12	12	11	12	12	12
PILOERECTION								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
BITE MARKS ON TAIL/PAWS								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
PALPEBRAL CLOSURE								
none	12	12	12	12	12	12	12	12
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
FUR APPEARANCE								
normal	12	12	12	12	12	12	12	12
slightly soiled	0	0	0	0	0	0	0	0
very soiled, crusty	0	0	0	0	0	0	0	0

TABLE 40 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
LACRIMATION								
none	12	12	12	12	12	12	12	12
slight	0	0	0	0	0	0	0	0
severe	0	0	0	0	0	0	0	0
SALIVATION								
none	12	12	12	12	12	12	12	12
slight (wet chin)	0	0	0	0	0	0	0	0
severe (active salivation, drooling)	0	0	0	0	0	0	0	0
EXOPHTHALMUS								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
OPEN FIELD AREA								
RIGHTING REFLEX								
present	12	12	12	12	12	12	12	12
slow	0	0	0	0	0	0	0	0
absent	0	0	0	0	0	0	0	0
EASE OF RESPIRATION								
normal	12	12	12	12	12	12	12	12
labored breathing	0	0	0	0	0	0	0	0
RATE OF RESPIRATION								
slow	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
rapid	0	0	0	0	0	0	0	0
POSTURE								
normal	12	12	12	12	12	12	12	12
abnormal	0	0	0	0	0	0	0	0
CONVULSIONS								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0

TABLE 40 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
TREMORS								
none	12	12	12	12	12	12	12	12
slight - paws	0	0	0	0	0	0	0	0
mild - limbs	0	0	0	0	0	0	0	0
severe - multiple sites	0	0	0	0	0	0	0	0
MUSCLE SPASMS								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
MUSCLE FASCICULATION								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
GROOMING								
normal or none	12	12	12	12	12	12	12	12
repetitive, stereotypy	0	0	0	0	0	0	0	0
GAIT/COORDINATION								
normal	12	12	12	12	12	12	12	12
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0
AROUSAL								
very low (stupor, little or no responsiveness)	0	0	0	0	0	0	0	0
low	1	0	1	0	0	3	1	1
normal (alert, exploratory movements)	11	12	11	12	12	9	11	11
high (slight excitement, tense, sudden movements)	0	0	0	0	0	0	0	0
VOCALIZATIONS								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	11	11	12	12
vocalizes only when handled	0	0	0	0	1	1	0	0

TABLE 40 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
PALPEBRAL CLOSURE								
none	12	12	12	12	12	12	12	12
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
DIARRHEA								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
POLYURIA								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
MANIPULATIONS								
APPROACH & TOUCH								
no reaction	0	0	0	0	0	0	0	0
normal	11	12	12	12	11	12	12	12
increased reaction (jumps away or attacks)	1	0	0	0	1	0	0	0
AUDITORY STIMULUS								
no reaction	0	0	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	12	12	12	12	12	12	12	12
exaggerated reaction (rat jumps, flips)	0	0	0	0	0	0	0	0
TAIL PINCH								
no response	0	0	0	0	0	0	0	0
normal (turns toward site)	12	12	12	12	9	12	10	12
exaggerated response	0	0	0	0	3	0	2	0
IN MOTOR ACTIVITY MONITOR								
PUPILLARY RESPONSE								
present	12	12	12	12	12	12	12	12
absent	0	0	0	0	0	0	0	0
DIARRHEA								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12

TABLE 40 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR MALE RATS

	BASELINE				WEEK 4			
GROUP	I	III	V	VII	I	III	V	VII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
POLYURIA								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
ADDITIONAL FINDINGS								
HEAD SHAKING								
present	0	0	0	1	0	0	0	0
absent	12	12	12	11	12	12	12	12

Statistical Methods: Cochran-Armitage test for trend.

There were no statistically significant trends from control at $p < 0.05$.

TABLE 41

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
HOME CAGE								
POSTURE								
limbs spread out or lying on one side	0	0	0	0	0	0	0	0
curled up,	2	3	3	1	1	1	0	2
sitting, standing or rearing normally, alert	10	9	9	11	11	11	12	10
jumping	0	0	0	0	0	0	0	0
PALPEBRAL CLOSURE								
eyelids wide open	10	9	9	12	12	11	12	11
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
rat appears to be sleeping	2	3	3	0	0	1	0	1
WRITHING								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
CIRCLING								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
BITING								
absent	12	12	12	12	12	12	12	12
biting others	0	0	0	0	0	0	0	0
biting cage	0	0	0	0	0	0	0	0
self mutilation	0	0	0	0	0	0	0	0
GAIT/COORDINATION								
normal	12	12	12	12	12	12	12	12
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0

TABLE 41 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
REMOVAL FROM CAGE								
EASE OF REMOVAL								
too easy (rat sits quietly, no resistance)	0	0	0	0	0	0	0	0
some resistance (rears, follows observer's hand)	12	12	12	12	12	12	12	12
difficult (runs around cage, may attack)	0	0	0	0	0	0	0	0
EASE OF HANDLING								
too easy	0	0	0	0	0	0	0	0
easy (alert, limbs pulled up against body)	12	12	12	12	12	12	12	12
difficult	0	0	0	0	0	0	0	0
MUSCLE TONE								
limp	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
rigid	0	0	0	0	0	0	0	0
VOCALIZATIONS								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
PILOERECTION								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
BITE MARKS ON TAIL/PAWS								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
PALPEBRAL CLOSURE								
none	12	12	12	12	12	12	12	12
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
FUR APPEARANCE								
normal	12	12	12	12	12	12	12	12
slightly soiled	0	0	0	0	0	0	0	0
very soiled, crusty	0	0	0	0	0	0	0	0

TABLE 41 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
LACRIMATION								
none	12	12	12	12	12	12	12	12
slight	0	0	0	0	0	0	0	0
severe	0	0	0	0	0	0	0	0
SALIVATION								
none	12	12	12	12	12	12	12	12
slight (wet chin)	0	0	0	0	0	0	0	0
severe (active salivation, drooling)	0	0	0	0	0	0	0	0
EXOPHTHALMUS								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
OPEN FIELD								
RIGHTING REFLEX								
present	12	12	12	12	11	12	12	12
slow	0	0	0	0	1	0	0	0
absent	0	0	0	0	0	0	0	0
RESPIRATION EASE								
normal	12	12	12	12	12	12	12	12
labored breathing	0	0	0	0	0	0	0	0
RATE OF RESPIRATION								
slow	0	0	0	0	0	0	0	0
normal	12	12	12	12	12	12	12	12
rapid	0	0	0	0	0	0	0	0
POSTURE								
normal	12	12	12	12	12	12	12	12
abnormal	0	0	0	0	0	0	0	0
CONVULSIONS								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0

TABLE 41 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
TREMORS								
none	12	12	12	12	12	12	12	12
slight - paws	0	0	0	0	0	0	0	0
mild - limbs	0	0	0	0	0	0	0	0
severe - multiple sites	0	0	0	0	0	0	0	0
MUSCLE SPASMS								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
MUSCLE FASCICULATION								
absent	12	12	12	12	12	12	12	12
present	0	0	0	0	0	0	0	0
GROOMING								
normal or none	12	12	12	12	12	12	12	12
repetitive, stereotypy	0	0	0	0	0	0	0	0
GAIT/COORDINATION								
normal	12	12	12	12	12	12	12	12
unbalanced, swaying, uncoordinated	0	0	0	0	0	0	0	0
ataxic	0	0	0	0	0	0	0	0
unable to move	0	0	0	0	0	0	0	0
AROUSAL								
very low (stupor, little or no responsiveness)	0	0	0	0	0	0	0	0
low	0	0	0	0	1	1	0	0
normal (alert, exploratory movements)	12	12	12	12	11	11	11	10
high (slight excitement, tense, sudden movements)	0	0	0	0	0	0	1	2
VOCALIZATIONS								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
vocalizes only when handled	0	0	0	0	0	0	0	0

TABLE 41 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
PALPEBRAL CLOSURE								
none	12	12	12	12	12	12	12	12
eyelids drooping (ptosis)	0	0	0	0	0	0	0	0
eyelids completely shut	0	0	0	0	0	0	0	0
DIARRHEA								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
POLYURIA								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
MANIPULATIONS								
APPROACH & TOUCH								
no reaction	0	0	0	0	0	0	0	0
normal	11	12	10	12	11	11	12	12
increased reaction (jumps away or attacks)	1	0	2	0	1	1	0	0
AUDITORY STIMULUS								
no reaction	0	0	0	0	0	0	0	0
normal reaction (rat flinches or flicks ear)	11	12	11	11	12	12	12	12
exaggerated reaction (rat jumps, flips)	1	0	1	1	0	0	0	0
TAIL PINCH								
no response	0	0	0	0	0	0	0	0
normal (turns toward site)	12	12	12	11	10	12	12	11
exaggerated response	0	0	0	1	2	0	0	1
IN MOTOR ACTIVITY MONITOR								
PUPILLARY RESPONSE								
normal	12	12	12	12	12	12	12	12
abnormal	0	0	0	0	0	0	0	0
DIARRHEA								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12

TABLE 41 (Continued)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY FINDINGS
FOR FEMALE RATS

	BASELINE				WEEK 4			
GROUP	II	IV	VI	VIII	II	IV	VI	VIII
DOSAGE (mg/kg/day)	0	5	25	100	0	5	25	100
NUMBER EXAMINED	12	12	12	12	12	12	12	12
POLYURIA								
present	0	0	0	0	0	0	0	0
absent	12	12	12	12	12	12	12	12
ADDITIONAL FINDINGS								
HEAD SHAKING								
present	0	0	1	0	0	0	0	0
absent	12	12	11	12	12	12	12	12
DEFORMED RIGHT REAR LEG								
present	0	0	0	0	0	0	1	0
absent	12	12	12	12	12	12	11	12

Statistical Methods: Cochran-Armitage test for trend.

There were no statistically significant trends from control at $p < 0.05$.

TABLE 42

MOTOR ACTIVITY ASSESSEMENT: MEAN DURATION OF MOVEMENT FOR MALE RATS (SEC)

		SUCCESSIVE 10-MINUTE INTERVALS						
	DOSAGE	1	2	3	4	5	6	TOTAL
GROUP	(mg/kg/day)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)
BASELINE								
I	0	385 (38)	274 (53)	158 (54)	94 (105)	41 (67)	5 (10)	958 (197)
III	5	363 (51)	291 (78)	199 (74)	129 (98)	59 (72)	26 (53)	1067 (337)
V	25	364 (52)	290 (60)	200 (52)	100 (97)	34 (71)	14 (23)	1002 (263)
VII	100	368 (40)	285 (56)	198 (51)	83 (76)	48 (68)	21 (44)	1003 (224)
WEEK 4								
I	0	420 (40)	309 (48)	250 (86)	177 (128)	95 (136)	99 (118)	1350 (403)
III	5	409 (48)	359 (52)	279 (82)	239 (65)	139 (109)	114 (141)	1539 (344)
V	25	413 (46)	324 (71)	252 (71)	213 (114)	114 (110)	126 (130)	1442 (322)
VII	100	419 (66)	328 (91)	303 (77)	246 (94)	161 (114)	86 (100)	1543 (353)

N = 12 rats per group

Statistical Methods: Shapiro-Wilk test for normality and Levene's test for homogeneity were performed. Repeated measures analysis of variance with linear contrasts or Jonckheere's trend test was used to identify which groups, if any, were significantly different from the control group. These tests were applied to Interval data and Total data.

There were no statistically significant differences or trends compared to control at $p < 0.05$.

TABLE 43

MOTOR ACTIVITY ASSESSEMENT: MEAN DURATION OF MOVEMENT FOR FEMALE RATS (SEC)

		SUCCESSIVE 10-MINUTE INTERVALS						
	DOSAGE	1	2	3	4	5	6	TOTAL
GROUP	(mg/kg/day)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)
BASELINE								
II	0	368 (47)	277 (72)	187 (134)	109 (119)	71 (117)	71 (104)	1083 (485)
IV	5	343 (54)	244 (82)	166 (106)	126 (93)	80 (79)	57 (78)	1016 (308)
VI	25	353 (46)	266 (98)	189 (81)	133 (97)	110 (102)	67 (74)	1117 (333)
VIII	100	360 (58)	273 (89)	192 (95)	125 (113)	93 (87)	50 (71)	1093 (349)
WEEK 4								
II	0	366 (70)	279 (85)	216 (85)	171 (79)	130 (86)	86 (85)	1248 (313)
IV	5	332 (60)	280 (66)	234 (68)	198 (83)	140 (77)	115 (96)	1300 (308)
VI	25	372 (45)	291 (65)	196 (92)	197 (76)	160 (84)	132 (95)	1347 (373)
VIII	100	395 (51)	301 (49)	246 (82)	180 (67)	181 (101)	124 (94)	1428 (296)

N = 12 rats per group

Statistical Methods: Shapiro-Wilk test for normality and Levene's test for homogeneity were performed. Repeated measures analysis of variance with linear contrasts was used to identify which groups, if any, were significantly different from the control group. These tests were applied to Interval data and Total data.

There were no statistically significant differences from control at $p < 0.05$.

TABLE 44

MOTOR ACTIVITY ASSESSEMENT: MEAN NUMBER OF MOVEMENTS FOR MALE RATS

		SUCCESSIVE 10-MINUTE INTERVALS						
	DOSAGE	1	2	3	4	5	6	TOTAL
GROUP	(mg/kg/day)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)
BASELINE								
I	0	141 (18)	139 (13)	112 (33)	65 (62)	36 (51)	8 (13)	501 (143)
III	5	141 (20)	142 (19)	120 (32)	84 (49)	46 (45)	23 (39)	555 (145)
V	25	142 (24)	138 (19)	131 (16)	70 (54)	27 (48)	16 (23)	524 (139)
VII	100	136 (16)	144 (17)	120 (35)	62 (49)	39 (49)	17 (28)	518 (133)
WEEK 4								
I	0	135 (14)	140 (15)	117 (34)	84 (43)	44 (46)	48 (49)	568 (102)
III	5	136 (19)	138 (17)	130 (30)	122 (30)	81 (54)	60 (56)	667 (148)
V	25	131 (20)	133 (23)	122 (20)	109 (46)	67 (61)	66 (63)	628 (151)
VII	100	131 (23)	138 (30)	129 (25)	117 (31)	85 (51)	52 (56)	652 (144)

N = 12 rats per group

Statistical Methods: Shapiro-Wilk test for normality and Levene's test for homogeneity were performed. Repeated measures analysis of variance with linear contrasts or Jonckheere's trend test was used to identify which groups, if any, were significantly different from the control group. These tests were applied to Interval data and Total data.

There were no statistically significant differences or trends compared to control at $p < 0.05$.

TABLE 45

MOTOR ACTIVITY ASSESSEMENT: MEAN NUMBER OF MOVEMENTS FOR FEMALE RATS

		SUCCESSIVE 10-MINUTE INTERVALS						
	DOSAGE	1	2	3	4	5	6	TOTAL
GROUP	(mg/kg/day)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)	MEAN (S.D.)
BASELINE								
II	0	143 (8)	140 (14)	98 (55)	69 (59)	41 (53)	47 (56)	539 (202)
IV	5	139 (13)	123 (35)	96 (46)	85 (53)	58 (49)	45 (50)	548 (170)
VI	25	139 (16)	132 (29)	113 (46)	90 (51)	74 (57)	57 (45)	605 (182)
VIII	100	138 (17)	135 (20)	104 (36)	81 (54)	64 (55)	42 (48)	564 (159)
WEEK 4								
II	0	135 (12)	134 (13)	117 (38)	109 (30)	90 (47)	60 (49)	645 (113)
IV	5	139 (17)	138 (21)	130 (17)	112 (36)	98 (45)	75 (54)	692 (122)
VI	25	140 (18)	138 (15)	114 (30)	117 (23)	97 (40)	83 (48)	690 (112)
VIII	100	139 (16)	141 (20)	119 (23)	112 (33)	106 (51)	84 (54)	700 (148)

N = 12 rats per group

Statistical Methods: Shapiro-Wilk test for normality and Levene's test for homogeneity were performed. Repeated measures analysis of variance with linear contrasts was used to identify which groups, if any, were significantly different from the control group. These tests were applied to Interval data and Total data.

There were no statistically significant differences from control at $p < 0.05$.

TABLE 46

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 5 mg/kg/day	Group V 25 mg/kg/day	Group VII 100 mg/kg/day
RBC ($x10^6/\mu L$)				
DAY 30	7.93	7.88	7.82	7.69
	0.34(9)	0.32(12)	0.32(12)	0.20(11)
HGB (g/dL)				
DAY 30	15.5	15.4	15.1	15.2
	0.4(9)	0.5(12)	0.7(12)	0.5(11)
HCT (%)				
DAY 30	48.6	48.1	47.7	47.3
	1.9(9)	1.8(12)	2.1(12)	1.5(11)
MCV (fl)				
DAY 30	61.4	61.0	61.1	61.5
	1.8(9)	1.7(12)	1.4(12)	1.6(11)
MCH (pg)				
DAY 30	19.5	19.5	19.4	19.7
	0.4(9)	0.5(12)	0.5(12)	0.5(11)
MCHC (g/dL)				
DAY 30	31.9	32.0	31.8	32.1
	0.5(9)	0.3(12)	0.4(12)	0.3(11)
RDW (%)				
DAY 30	11.0	11.1	11.3	11.3
	0.3(9)	0.4(12)	0.6(12)	0.4(11)
ARET ($x10^3/\mu L$)				
DAY 30	174.2	198.9	200.7	186.9
	41.3(9)	23.5(12)	23.9(12)	26.2(11)
PLT ($x10^3/\mu L$)				
DAY 30	1207	1106	1150	1138
	90(8)	137(7)	129(12)	113(8)
WBC ($x10^3/\mu L$)				
DAY 30	13.14	14.59	14.08	12.89
	3.62(9)	2.86(12)	2.98(12)	2.26(11)
ANEU ($x10^3/\mu L$)				
DAY 30	1.53	1.85	2.09	1.84
	0.64(9)	0.59(12)	0.96(12)	0.58(11)
ALYM ($x10^3/\mu L$)				
DAY 30	11.14	12.01	11.43	10.53
	3.10(9)	2.46(12)	2.47(12)	1.95(11)

TABLE 46 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 5 mg/kg/day	Group V 25 mg/kg/day	Group VII 100 mg/kg/day
AMON (x10³/µL)				
DAY 30	0.22 0.10(9)	0.47* 0.23(12)	0.33 0.12(12)	0.27 0.09(11)
AEOS (x10³/µL)				
DAY 30	0.11 0.09(9)	0.13 0.04(12)	0.10 0.04(12)	0.13 0.07(11)
ABAS (x10³/µL)				
DAY 30	0.06 0.04(9)	0.05 0.04(12)	0.06 0.02(12)	0.05 0.01(11)
ALUC (x10³/µL)				
DAY 30	0.08 0.04(9)	0.08 0.06(12)	0.07 0.03(12)	0.07 0.03(11)
NRBC (/100 WBC)				
DAY 30	-	1 NC(1)	-	-

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.

TABLE 47

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 5 mg/kg/day	Group VI 25 mg/kg/day	Group VIII 100 mg/kg/day
RBC ($x10^6/\mu L$)				
DAY 31	7.88	7.83	7.93	7.90
	0.19(12)	0.41(12)	0.27(12)	0.23(12)
HGB (g/dL)				
DAY 31	15.8	15.6	15.4	15.3
	0.6(12)	0.6(12)	0.6(12)	0.5(12)
HCT (%)				
DAY 31	47.7	46.9	46.6	46.4
	1.9(12)	2.0(12)	1.3(12)	1.3(12)
MCV (fl)				
DAY 31	60.5	59.9	58.7*	58.8*
	2.5(12)	1.8(12)	1.3(12)	1.1(12)
MCH (pg)				
DAY 31	20.1	19.9	19.4@	19.3@
	0.9(12)	0.8(12)	0.3(12)	0.4(12)
MCHC (g/dL)				
DAY 31	33.2	33.2	33.0	32.9
	0.5(12)	0.7(12)	0.7(12)	0.6(12)
RDW (%)				
DAY 31	10.6	10.5	10.3	10.5
	0.4(12)	0.3(12)	0.5(12)	0.4(12)
ARET ($x10^3/\mu L$)				
DAY 31	208.9	203.2	170.7	202.0
	39.0(12)	23.1(12)	42.8(12)	50.2(12)
PLT ($x10^3/\mu L$)				
DAY 31	1224	1248	1167	1245
	182(6)	128(8)	94(10)	141(6)
WBC ($x10^3/\mu L$)				
DAY 31	9.89	9.07	9.08	8.12
	2.52(12)	2.55(12)	1.93(12)	1.94(12)
ANEU ($x10^3/\mu L$)				
DAY 31	0.67	0.60	0.70	0.72
	0.26(12)	0.26(12)	0.34(12)	0.29(12)
ALYM ($x10^3/\mu L$)				
DAY 31	8.81	8.00	7.97	7.06
	2.36(12)	2.45(12)	1.62(12)	1.78(12)

TABLE 47 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 5 mg/kg/day	Group VI 25 mg/kg/day	Group VIII 100 mg/kg/day
AMON ($x10^3/\mu L$)				
DAY 31	0.18	0.30	0.23	0.17
	0.11(12)	0.33(12)	0.16(12)	0.09(12)
AEOS ($x10^3/\mu L$)				
DAY 31	0.13	0.10	0.11	0.09
	0.04(12)	0.04(12)	0.10(12)	0.03(12)
ABAS ($x10^3/\mu L$)				
DAY 31	0.05	0.03*	0.03*	0.03*
	0.03(12)	0.02(12)	0.02(12)	0.02(12)
ALUC ($x10^3/\mu L$)				
DAY 31	0.06	0.05	0.06	0.05
	0.03(12)	0.03(12)	0.04(12)	0.02(12)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

TABLE 48

SUMMARY OF COAGULATION VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 5 mg/kg/day	Group V 25 mg/kg/day	Group VII 100 mg/kg/day
PT (seconds)				
DAY 30	15.5 1.1(12)	15.3 1.0(12)	15.9 1.6(12)	15.7 0.5(12)
APTT (seconds)				
DAY 30	17.3 2.1(12)	17.9 2.0(12)	18.0 2.0(12)	17.8 1.4(12)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

There were no statistically significant differences from control at $p < 0.05$.

TABLE 49

SUMMARY OF COAGULATION VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 5 mg/kg/day	Group VI 25 mg/kg/day	Group VIII 100 mg/kg/day
PT (seconds)				
DAY 31	15.8 0.5(12)	15.7 0.5(12)	15.3 0.4(11)	15.6 0.6(12)
APTT (seconds)				
DAY 31	16.1 1.7(12)	16.4 2.7(12)	16.3 2.1(11)	16.2 2.2(12)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

There were no statistically significant differences from control at $p < 0.05$.

TABLE 50

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 5 mg/kg/day	Group V 25 mg/kg/day	Group VII 100 mg/kg/day
AST (U/L)				
DAY 30	92	88	86	82
	12(12)	12(12)	11(12)	16(12)
ALT (U/L)				
DAY 30	30	29	29	28
	5(12)	4(12)	4(12)	4(12)
SDH (U/L)				
DAY 30	14.3	14.2	12.6	12.5
	3.8(12)	2.7(12)	3.7(12)	3.6(11)
ALKP (U/L)				
DAY 30	185	168	180	160
	37(12)	36(12)	40(12)	33(12)
BILI (mg/dL)				
DAY 30	0.11	0.10	0.10	0.07@
	0.03(12)	0.03(12)	0.04(12)	0.03(12)
BUN (mg/dL)				
DAY 30	12	13	13	11
	2(12)	2(12)	2(12)	1(12)
CREA (mg/dL)				
DAY 30	0.35	0.34	0.35	0.33
	0.04(12)	0.05(12)	0.05(12)	0.04(12)
CHOL (mg/dL)				
DAY 30	51	50	54	48
	10(12)	10(12)	8(12)	9(12)
TRIG (mg/dL)				
DAY 30	41	42	41	47
	23(12)	16(12)	23(12)	16(12)
GLUC (mg/dL)				
DAY 30	123	117	106	106
	31(12)	25(12)	6(12)	14(12)
TP (g/dL)				
DAY 30	6.9	6.7	6.8	6.7
	0.3(12)	0.3(12)	0.2(12)	0.3(12)
ALB (g/dL)				
DAY 30	4.7	4.4*	4.5	4.5
	0.2(12)	0.2(12)	0.2(12)	0.2(12)

TABLE 50 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg/day	Group III 5 mg/kg/day	Group V 25 mg/kg/day	Group VII 100 mg/kg/day
GLOB (g/dL)				
DAY 30	2.3	2.2	2.3	2.2
	0.2(12)	0.2(12)	0.2(12)	0.3(12)
CALC (mg/dL)				
DAY 30	11.6	11.4	11.3	11.2*
	0.3(12)	0.3(12)	0.2(12)	0.3(12)
IPHS (mg/dL)				
DAY 30	9.9	9.8	9.8	9.7
	1.6(12)	0.8(12)	1.1(12)	1.1(12)
NA (mmol/L)				
DAY 30	151.4	151.4	152.4	151.5
	2.1(12)	2.5(12)	2.2(12)	2.3(12)
K (mmol/L)				
DAY 30	6.16	6.28	6.27	6.15
	0.57(12)	0.58(12)	0.46(12)	0.45(12)
CL (mmol/L)				
DAY 30	105.6	105.4	105.8	105.2
	2.2(12)	1.6(12)	2.2(12)	1.6(12)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

TABLE 51

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 5 mg/kg/day	Group VI 25 mg/kg/day	Group VIII 100 mg/kg/day
AST (U/L)				
DAY 31	92	83	99	86
	15(12)	16(12)	37(12)	16(12)
ALT (U/L)				
DAY 31	24	23	31	23
	2(12)	3(12)	19(12)	3(12)
SDH (U/L)				
DAY 31	14.4	12.2	16.0	13.1
	3.4(12)	3.0(12)	6.2(12)	3.6(12)
ALKP (U/L)				
DAY 31	108	95	86*	96
	17(12)	24(12)	22(12)	21(12)
BILI (mg/dL)				
DAY 31	0.15	0.15	0.14	0.11*
	0.04(12)	0.03(12)	0.02(12)	0.03(12)
BUN (mg/dL)				
DAY 31	15	15	15	14
	1(12)	2(12)	2(12)	2(12)
CREA (mg/dL)				
DAY 31	0.37	0.38	0.40	0.38
	0.06(12)	0.05(12)	0.08(12)	0.04(12)
CHOL (mg/dL)				
DAY 31	54	55	57	62
	13(12)	15(12)	12(12)	11(12)
TRIG (mg/dL)				
DAY 31	24	28	28	26
	6(12)	7(12)	9(12)	8(12)
GLUC (mg/dL)				
DAY 31	111	116	116	115
	9(12)	20(12)	14(12)	12(12)
TP (g/dL)				
DAY 31	6.8	6.9	7.2@	6.9
	0.4(12)	0.4(12)	0.6(12)	0.3(12)
ALB (g/dL)				
DAY 31	4.9	5.1	5.2	5.0
	0.3(12)	0.2(12)	0.4(12)	0.2(12)

TABLE 51 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR FEMALE RATS

	Group II 0 mg/kg/day	Group IV 5 mg/kg/day	Group VI 25 mg/kg/day	Group VIII 100 mg/kg/day
GLOB (g/dL)				
DAY 31	1.8	1.8	2.0	1.9
	0.2(12)	0.3(12)	0.2(12)	0.2(12)
CALC (mg/dL)				
DAY 31	11.0	11.2	11.2	11.1
	0.4(12)	0.4(12)	0.5(12)	0.5(12)
IPHS (mg/dL)				
DAY 31	7.9	8.1	8.1	7.9
	0.8(12)	1.0(12)	1.6(12)	0.7(12)
NA (mmol/L)				
DAY 31	149.4	149.6	150.2	149.8
	2.4(12)	1.8(12)	2.5(12)	2.5(12)
K (mmol/L)				
DAY 31	6.14	5.95	6.00	6.20
	0.57(12)	0.38(12)	0.60(12)	0.40(12)
CL (mmol/L)				
DAY 31	105.6	106.0	107.0	105.6
	2.4(12)	2.3(12)	2.8(12)	1.4(12)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

TABLE 52

MEAN FINAL BODY AND ORGAN WEIGHTS (grams) - SUBCHRONIC ADULT MALE

Group:	I	III	V	VII
Dosage(mg/kg/day)	0	5	25	100
Final Body Weight	397.0	424.8*	410.0	403.9
	25.2(12)	27.0(12)	24.4(12)	23.5(12)
Liver	12.104	13.243	12.870	13.496#
	0.974(12)	1.053(12)	1.127(12)	0.559(12)
Kidneys	3.224	3.639#	3.779#	3.853#
	0.210(12)	0.200(12)	0.310(12)	0.181(12)
Lungs	1.973	1.894	1.888	1.823
	0.348(12)	0.178(12)	0.143(12)	0.122(12)
Heart	1.520	1.551	1.517	1.433
	0.113(12)	0.144(12)	0.124(12)	0.083(12)
Spleen	0.650	0.817	0.690	0.675
	0.114(12)	0.127(12)	0.125(12)	0.093(12)
Thymus	0.534	0.485	0.484	0.443
	0.112(12)	0.143(12)	0.103(12)	0.087(12)
Adrenal Glands	0.060	0.064	0.063	0.062
	0.007(12)	0.007(12)	0.008(12)	0.006(12)
Testes	3.132	3.373	3.203	3.270
	0.201(12)	0.235(12)	0.297(12)	0.223(12)
Epididymides	1.174	1.225	1.161	1.169
	0.077(12)	0.114(12)	0.105(12)	0.079(12)
Brain	2.031	2.030	2.053	2.014
	0.085(12)	0.090(12)	0.111(12)	0.066(12)

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS (grams) - SUBCHRONIC ADULT MALE

Group:	I	III	V	VII
Dosage(mg/kg/day)	0	5	25	100
Liver/Final Body * 100	3.048	3.117	3.137	3.347#
	0.149(12)	0.158(12)	0.160(12)	0.140(12)
Kidneys/Final Body * 100	0.813	0.858#	0.924#	0.955#
	0.039(12)	0.036(12)	0.082(12)	0.046(12)
Lungs/Final Body * 100	0.501	0.446	0.461	0.452
	0.105(12)	0.037(12)	0.031(12)	0.034(12)
Heart/Final Body * 100	0.384	0.365	0.370	0.355#
	0.031(12)	0.028(12)	0.022(12)	0.015(12)
Spleen/Final Body * 100	0.163	0.192	0.168	0.167
	0.021(12)	0.026(12)	0.029(12)	0.022(12)
Thymus/Final Body * 100	0.135	0.114	0.118	0.110#
	0.026(12)	0.029(12)	0.024(12)	0.018(12)
Adrenal Glands/Final Body * 100	0.015	0.015	0.015	0.015
	0.002(12)	0.002(12)	0.002(12)	0.002(12)
Testes/Final Body * 100	0.791	0.795	0.782	0.811
	0.062(12)	0.039(12)	0.067(12)	0.059(12)
Epididymides/Final Body * 100	0.297	0.288	0.283	0.290
	0.027(12)	0.018(12)	0.022(12)	0.024(12)
Brain/Final Body * 100	0.513	0.479	0.502	0.500
	0.037(12)	0.020(12)	0.029(12)	0.037(12)

TABLE 52 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS (grams) - SUBCHRONIC ADULT MALE

Group:	I	III	V	VII
Dosage(mg/kg/day)	0	5	25	100
Liver/Brain * 100	597.038	652.118	628.403	670.874#
	54.571(12)	40.990(12)	59.815(12)	34.279(12)
Kidneys/Brain * 100	158.967	179.409#	184.512#	191.580#
	11.174(12)	10.062(12)	16.777(12)	11.702(12)
Lungs/Brain * 100	97.236	93.263	92.093	90.649
	17.349(12)	7.277(12)	6.628(12)	7.239(12)
Heart/Brain * 100	74.966	76.406	74.071	71.240
	6.236(12)	6.135(12)	6.549(12)	4.561(12)
Spleen/Brain * 100	32.084	40.178	33.723	33.554
	6.067(12)	5.634(12)	6.305(12)	4.710(12)
Thymus/Brain * 100	26.307	23.786	23.545	22.034#
	5.383(12)	6.451(12)	4.789(12)	4.390(12)
Adrenal Glands/Brain * 100	2.954	3.149	3.051	3.074
	0.292(12)	0.373(12)	0.355(12)	0.287(12)
Testes/Brain * 100	154.449	166.170	156.288	162.706
	10.778(12)	9.201(12)	14.932(12)	14.259(12)
Epididymides/Brain * 100	57.906	60.332	56.564	58.196
	4.087(12)	4.684(12)	4.347(12)	5.157(12)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant trend at p < 0.05 by Jonckheere-Terpstra test.

* Parametric comparison to control (Dunnett/Tamhane-Dunnett) significant.

TABLE 53

MEAN FINAL BODY AND ORGAN WEIGHTS (grams) – SUBCHRONIC ADULT FEMALE

Group:	II	IV	VI	VIII
Dosage(mg/kg/day)	0	5	25	100
Final Body Weight	233.3 15.7(12)	239.7 20.3(12)	231.6 21.8(12)	227.1 13.9(12)
Liver	7.007 0.572(12)	7.369 0.849(12)	7.343 0.990(12)	7.730# 0.704(12)
Kidneys	1.996 0.219(12)	2.047 0.149(12)	2.025 0.177(12)	2.079 0.160(12)
Lungs	1.336 0.115(12)	1.436 0.132(12)	1.348 0.123(12)	1.328 0.114(12)
Heart	0.895 0.097(12)	0.959 0.105(12)	0.905 0.105(12)	0.901 0.058(12)
Spleen	0.512 0.069(12)	0.503 0.053(12)	0.454# 0.058(12)	0.465# 0.031(12)
Thymus	0.348 0.067(12)	0.358 0.067(12)	0.374 0.087(12)	0.349 0.048(12)
Adrenal Glands	0.075 0.008(12)	0.076 0.010(12)	0.076 0.009(12)	0.075 0.009(12)
Ovaries	0.133 0.012(12)	0.137 0.017(12)	0.134 0.017(12)	0.142 0.029(12)
Uterus	0.601 0.184(12)	0.579 0.121(12)	0.647 0.244(12)	0.658 0.281(12)
Brain	1.876 0.093(12)	1.938 0.078(12)	1.904 0.090(12)	1.899 0.073(12)

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS (grams) – SUBCHRONIC ADULT FEMALE

Group:	II	IV	VI	VIII
Dosage(mg/kg/day)	0	5	25	100
Liver/Final Body * 100	3.005	3.073	3.168	3.403#
	0.191(12)	0.208(12)	0.289(12)	0.226(12)
Kidneys/Final Body * 100	0.855	0.857	0.876	0.915#
	0.064(12)	0.062(12)	0.045(12)	0.030(12)
Lungs/Final Body * 100	0.573	0.600	0.583	0.585
	0.033(12)	0.035(12)	0.032(12)	0.034(12)
Heart/Final Body * 100	0.383	0.400	0.391	0.397
	0.028(12)	0.032(12)	0.031(12)	0.019(12)
Spleen/Final Body * 100	0.220	0.211	0.196	0.205
	0.032(12)	0.025(12)	0.019(12)	0.014(12)
Thymus/Final Body * 100	0.149	0.150	0.162	0.154
	0.024(12)	0.029(12)	0.036(12)	0.022(12)
Adrenal Glands/Final Body * 100	0.032	0.032	0.033	0.033
	0.004(12)	0.004(12)	0.003(12)	0.004(12)
Ovaries/Final Body * 100	0.057	0.057	0.058	0.063
	0.006(12)	0.008(12)	0.008(12)	0.012(12)
Uterus/Final Body * 100	0.259	0.244	0.279	0.290
	0.084(12)	0.063(12)	0.096(12)	0.127(12)
Brain/Final Body * 100	0.806	0.812	0.827	0.838
	0.053(12)	0.055(12)	0.064(12)	0.049(12)

TABLE 53 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS (grams) – SUBCHRONIC ADULT FEMALE

Group:	II	IV	VI	VIII
Dosage(mg/kg/day)	0	5	25	100
Liver/Brain * 100	373.575	379.673	384.920	407.601#
	23.614(12)	34.970(12)	41.908(12)	39.963(12)
Kidneys/Brain * 100	106.346	105.595	106.307	109.524
	9.881(12)	5.957(12)	7.204(12)	7.774(12)
Lungs/Brain * 100	71.298	74.077	70.792	69.989
	6.213(12)	5.902(12)	4.946(12)	5.520(12)
Heart/Brain * 100	47.734	49.439	47.499	47.485
	4.536(12)	4.557(12)	4.394(12)	3.015(12)
Spleen/Brain * 100	27.333	25.913	23.817#	24.524#
	3.792(12)	2.339(12)	2.857(12)	1.531(12)
Thymus/Brain * 100	18.556	18.496	19.639	18.428
	3.428(12)	3.564(12)	4.458(12)	2.771(12)
Adrenal Glands/Brain * 100	4.002	3.909	3.966	3.923
	0.347(12)	0.413(12)	0.386(12)	0.443(12)
Ovaries/Brain * 100	7.087	7.044	7.042	7.452
	0.601(12)	0.867(12)	0.969(12)	1.337(12)
Uterus/Brain * 100	32.106	29.933	34.252	34.541
	9.615(12)	6.592(12)	13.524(12)	14.350(12)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant trend at p < 0.05 by Jonckheere-Terpstra test.

TABLE 54

MEAN FINAL BODY AND ORGAN WEIGHTS (grams) – SATELLITE ADULT FEMALE

Group:	II-0	IV-0	VI-0	VIII-0
Dosage(mg/kg/day)	0	5	25	100
Final Body Weight	302.8	311.0	307.5	307.5
	16.9(12)	24.4(12)	26.8(12)	22.3(12)
Liver	12.623	13.038	13.556	14.652#
	1.533(12)	1.436(12)	1.736(12)	1.765(12)
Kidneys	2.343	2.391	2.529	2.415
	0.211(12)	0.119(12)	0.306(12)	0.188(12)
Lungs	1.479	1.474	1.471	1.447
	0.086(12)	0.158(12)	0.113(12)	0.105(12)
Ovaries	0.135	0.127	0.147	0.138
	0.017(12)	0.012(12)	0.028(12)	0.021(12)
Uterus	0.678	0.716	0.725	0.645
	0.101(12)	0.101(12)	0.127(12)	0.145(12)
Brain	1.904	2.129	1.980	1.878
	0.075(12)	0.570(12)	0.119(12)	0.056(12)

TABLE 54 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS (grams) – SATELLITE ADULT FEMALE

Group:	II-0	IV-0	VI-0	VIII-0
Dosage(mg/kg/day)	0	5	25	100
Liver/Final Body * 100	4.158	4.191	4.415	4.761#
	0.344(12)	0.322(12)	0.495(12)	0.411(12)
Kidneys/Final Body * 100	0.773	0.772	0.826	0.787
	0.046(12)	0.060(12)	0.100(12)	0.052(12)
Lungs/Final Body * 100	0.489	0.474	0.480	0.472
	0.034(12)	0.032(12)	0.033(12)	0.035(12)
Ovaries/Final Body * 100	0.045	0.041	0.048	0.045
	0.006(12)	0.004(12)	0.009(12)	0.006(12)
Uterus/Final Body * 100	0.224	0.231	0.239	0.210
	0.036(12)	0.036(12)	0.054(12)	0.049(12)
Brain/Final Body * 100	0.630	0.683	0.648	0.613
	0.034(12)	0.150(12)	0.063(12)	0.044(12)

TABLE 54 (Continued)

MEAN FINAL BODY AND ORGAN WEIGHTS (grams) – SATELLITE ADULT FEMALE

Group:	II-0	IV-0	VI-0	VIII-0
Dosage(mg/kg/day)	0	5	25	100
Liver/Brain * 100	661.894	636.645	685.132	781.368#
	66.980(12)	125.651(12)	86.818(12)	99.784(12)
Kidneys/Brain * 100	123.089	116.444	127.791	128.811
	10.992(12)	17.643(12)	13.517(12)	11.752(12)
Lungs/Brain * 100	77.825	71.228	74.441	77.105
	6.148(12)	10.186(12)	6.242(12)	5.836(12)
Ovaries/Brain * 100	7.104	6.203	7.445	7.375
	0.977(12)	1.121(12)	1.419(12)	1.191(12)
Uterus/Brain * 100	35.677	34.973	36.949	34.528
	5.624(12)	7.578(12)	8.041(12)	8.261(12)

Data summarized as: Mean
Standard Deviation (n)

Statistically significant trend at p < 0.05 by Jonckheere-Terpstra test.

TABLE 55

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS - SUBCHRONIC ADULTS

	GROUP DESIGNATION:	I	III	V	VII
	DOSE (mg/kg/day):	0	5	25	100
SITE/LESION:	NUMBER IN GROUP:	12	12	12	12
LUNGS					
DISCOLORATION		0	0	1	0
URINARY BLADDER					
CALCULUS		0	0	1	0
KIDNEYS					
DILATATION		0	1	2	0
DISCOLORATION		0	1	5	8

NOTE:
- INCIDENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TABLE 56

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS - SUBCHRONIC ADULTS

	GROUP DESIGNATION:	II	IV	VI	VIII
	DOSE (mg/kg/day):	0	5	25	100
SITE/LESION:	NUMBER IN GROUP:	12	12	12	12
STOMACH					
ULCER/EROSION		0	0	1	0
LONG BONE					
FRACTURE		0	0	1	0
SKIN					
ALOPECIA		1	1	1	0

NOTE:
- INCIDENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TABLE 57

INCIDENCES OF GROSS OBSERVATIONS IN FEMALE RATS - SATELLITE ADULTS

	GROUP DESIGNATION:	II-0	IV-0	VI-0	VIII-0
	DOSE (mg/kg/day):	0	5	25	100
SITE/LESION:	NUMBER IN GROUP:	12	12	12	12
STOMACH					
DISCOLORATION		0	1	0	0
UTERUS					
DILATATION		0	0	0	1
VAGINA					
DILATATION		0	0	0	1
SKIN					
ALOPECIA		1	1	0	0

NOTE:
- INCIDENCES REFLECT THE NUMBER OF ANIMALS WITH A GIVEN LESION.

TABLE 58

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	I	III	V	VII
		DOSE (mg/kg/day):	0	5	25	100
		NUMBER IN GROUP:	12	12	12	12
DIGESTIVE SYSTEM						
LIVER			12	12	12	12
AGGREGATES, LYMPHOID, PERIPORTAL			2 (-,2,-,-,-)	3 (-,3,-,-,-)	2 (-,2,-,-,-)	2 (-,2,-,-,-)
FATTY CHANGE, MEDIAN CLEFT			-	-	1 (-,1,-,-,-)	-
FIBROSIS, BILIARY			-	1 (-,1,-,-,-)	-	1 (-,1,-,-,-)
HEMATOPOIESIS, INCREASED EXTRAMEDULLARY			-	-	3 (-,3,-,-,-)	-
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR			-	-	-	10 (,1, , ,) (-,0,-,-,-)
INFLAMMATION, SUBACUTE/CHRONIC			9 (, , , ,) (-,8,1,-,-)	12 (,1, , ,) (-,2,-,-,-)	11 (,1, , ,) (-,0,1,-,-)	10 (, , , ,) (-,9,1,-,-)
NECROSIS, COAGULATIVE, FOCAL			1 (-,1,-,-,-)	-	-	-
PANCREAS			12	0	0	12
AGGREGATES, LYMPHOID			1 (-,1,-,-,-)	-	-	-
TONGUE			12	0	0	12
ESOPHAGUS			12	0	0	12
DEGENERATION, MUSCULAR, FOCAL			-	-	-	1 (-,1,-,-,-)
INFLAMMATION, SUBACUTE/CHRONIC			1 (-,1,-,-,-)	-	-	-
STOMACH			12	0	0	12
DUODENUM			12	0	0	12
JEJUNUM			12	0	0	12
ILEUM			12	0	0	12
PEYER'S PATCH NOT PRESENT			-	-	-	2 (2,-,-,-,-)
PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)			4 (4,-,-,-,-)	-	-	2 (2,-,-,-,-)

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I	DOSE (mg/kg/day): 0	NUMBER IN GROUP: 12	III 5 12	V 25 12	VII 100 12
DIGESTIVE SYSTEM (Cont'd)							
CECUM		12		0	0	12	
CELLULARITY INCREASED, LAMINA PROPRIA		4	(-,3,1,-,-)	-	-	3	(-,3,-,-,-)
COLON		12		0	0	12	
RECTUM		12		0	0	12	
URINARY SYSTEM							
KIDNEYS		12		12	12	12	
AGGREGATES, LYMPHOID		5	(-,5,-,-,-)	2	(-,2,-,-,-)	7 (-,7,-,-,-)	3 (-,3,-,-,-)
CYST		1	(-,1,-,-,-)	-		1 (-,1,-,-,-)	1 (-,-,1,-,-)
HYALINE DROPLETS, INCREASED		-		12	(, , , ,) (-,6,6,-,-)	12 (, , , ,) (-,-,6,6,-)	12 (, , ,1,) (-,-,-,2,-)
HYDRONEPHROSIS, BILATERAL		-		2	(-,2,-,-,-)	1 (-,1,-,-,-)	-
HYDRONEPHROSIS, UNILATERAL		-		2	(-,1,1,-,-)	2 (-,2,-,-,-)	-
NEPHROPATHY, CHRONIC PROGRESSIVE		3	(-,3,-,-,-)	8	(-,8,-,-,-)	8 (-,8,-,-,-)	7 (-,7,-,-,-)
PYELONEPHRITIS, BILATERAL		-		-		1 (-,-,-,1,-)	-
URINARY BLADDER		12		0		1	12
CALCULUS		-		-		1 (1,-,-,-,-)	-
HYPERPLASIA, MUCOSAL		-		-		1 (-,-,-,-,1)	-
INFLAMMATION, SUBACUTE/CHRONIC		-		-		1 (-,-,-,1,-)	-

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	I	III	V	VII
		DOSE (mg/kg/day):	0	5	25	100
		NUMBER IN GROUP:	12	12	12	12
RESPIRATORY SYSTEM						
NOSE			12	0	0	12
INFLAMMATION, GINGIVAL			1 (-,1,-,-,-)	-	-	1 (-,1,-,-,-)
PHARYNX/LARYNX			12	0	0	12
TRACHEA			12	0	0	12
INFLAMMATION, SUBACUTE/CHRONIC			-	-	-	1 (-,1,-,-,-)
LUNGS			12	0	1	12
HEMORRHAGE			4 (-,3,1,-,-)	-	1 (-,-,1,-,-)	3 (-,3,-,-,-)
HISTIOCYTOSIS, ALVEOLAR			2 (-,1,1,-,-)	-	-	2 (-,2,-,-,-)
INFLAMMATION, ALVEOLAR			1 (-,1,-,-,-)	-	1 (-,1,-,-,-)	-
INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR			-	-	-	2 (-,2,-,-,-)
THROMBUS/THROMBI, VASCULAR			1 (-,1,-,-,-)	-	-	-
CARDIOVASCULAR SYSTEM						
HEART			12	0	0	12
INFLAMMATION, SUBACUTE/CHRONIC			5 (-,5,-,-,-)	-	-	4 (-,4,-,-,-)
AORTA			12	0	0	12

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I	DOSE (mg/kg/day): 0	NUMBER IN GROUP: 12	III 5 12	V 25 12	VII 100 12
HEMATOPOIETIC SYSTEM							
BONE MARROW		12		0	0	12	
THYMUS		12		0	0	12	
HEMORRHAGE		3	(-,3,-,-,-)	-	-	5	(-,5,-,-,-)
SPLEEN		12		0	0	12	
MANDIBULAR LYMPH NODE		12		0	0	12	
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS		5	(-,1,4,-,-)	-	-	3	(-,3,-,-,-)
MEDIASTINAL LYMPH NODE		11		0	0	12	
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS		9	(-,2,7,-,-)	-	-	6	(-,3,3,-,-)
MESENTERIC LYMPH NODE		12		0	0	12	
ENDOCRINE SYSTEM							
PITUITARY GLAND		12		0	0	12	
ADRENAL GLANDS		12		0	0	12	
THYROID GLAND		12		12	12	12	
AGGREGATES, LYMPHOID		-		1	(-,1,-,-,-)	-	-
ECTOPIC THYMUS TISSUE		1	(1,-,-,-,-)	3	(3,-,-,-,-)	-	-
HYPERTROPHY, FOLLICULAR CELL		2	(-,2,-,-,-)	2	(-,2,-,-,-)	5	(-,3,2,-,-) 7 (-,6,1,-,-)
PARATHYROID GLAND		11		0	0	10	

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	I	III	V	VII
		DOSE (mg/kg/day):	0	5	25	100
		NUMBER IN GROUP:	12	12	12	12
NERVOUS SYSTEM						
BRAIN			12	0	0	12
SPINAL CORD			12	0	0	12
SCIATIC NERVE			12	0	0	12
EYES			12	0	0	12
EROSION/ULCER, CORNEAL			1 (-,1,-,-,-)	-	-	1 (-,1,-,-,-)
INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE)			5 (-,4,1,-,-)	-	-	5 (-,3,2,-,-)
ONE OF PAIRED ORGAN MISSING			1 (1,-,-,-,-)	-	-	1 (1,-,-,-,-)
OPTIC NERVE NOT PRESENT, BILATERAL			2 (2,-,-,-,-)	-	-	3 (3,-,-,-,-)
OPTIC NERVE NOT PRESENT, UNILATERAL			3 (3,-,-,-,-)	-	-	2 (2,-,-,-,-)
MUSCULOSKELETAL SYSTEM						
FEMUR/KNEE JOINT			12	0	0	12
HEMORRHAGE, PERIOSTEAL			-	-	-	1 (-,1,-,-,-)
STERNUM			12	0	0	12
SKELETAL MUSCLE			12	0	0	12
AGGREGATES, LYMPHOID			1 (-,1,-,-,-)	-	-	-
REPRODUCTIVE SYSTEM						
TESTES			12	0	1	12
EPIDIDYMIDES			12	0	1	12
AGGREGATES, LYMPHOID			8 (-,8,-,-,-)	-	-	7 (-,7,-,-,-)
GRANULOMA, SPERM			-	-	-	1 (-,-,1,-,-)

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: I	DOSE (mg/kg/day): 0	NUMBER IN GROUP: 12	III 5 12	V 25 12	VII 100 12
REPRODUCTIVE SYSTEM (Cont'd)							
PROSTATE		12		0	1		12	
AGGREGATES, LYMPHOID		3	(-,-,2,1,-)	-	1	(-,1,-,-,-)	3	(-,-,2,1,-)
CYST		2	(-,1,1,-,-)	-	-		1	(-,-,1,-,-)
SEMINAL VESICLES		12		0	1		12	
COAGULATING GLANDS		12		0	1		12	
INTEGUMENTARY SYSTEM							
SKIN		12		0	0		12	
SALIVARY GLANDS		12		0	0		12	
AGGREGATES, LYMPHOID		-		-	-		1	(-,-,1,-,-)
EXORBITAL LACRIMAL GLANDS		12		0	0		12	
AGGREGATES, LYMPHOID		1	(-,1,-,-,-)	-	-		2	(-,2,-,-,-)
MISCELLANEOUS							
OTHER		0		0	0		0	
CAUSE OF DEATH		12		0	0		12	
SACRIFICED BY DESIGN		12		-	-		12	
TOTAL ANIMALS WITH PRIMARY TUMORS		0		0	0		0	
TOTAL ANIMALS WITH BENIGN TUMORS		0		0	0		0	
TOTAL ANIMALS WITH MALIGNANT TUMORS		0		0	0		0	

TABLE 58 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS – SUBCHRONIC ADULTS

		GROUP DESIGNATION:	I	III	V	VII
	LESION GRADES	DOSE (mg/kg/day):	0	5	25	100
TISSUE/LESION	(P,1,2,3,4)	NUMBER IN GROUP:	12	12	12	12

NOTES:

- THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
- LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. DOUBLE DIGIT NUMBERS ARE EXPRESSED VERTICALLY, FOR EXAMPLE: (,1, ,1,1) MEANS NO LESIONS (-,0,6,1,5) WERE GRADED "PRESENT", 10 LESIONS WERE "MINIMAL", 6 LESIONS WERE "MILD", 11 LESIONS WERE "MODERATE", AND 15 LESIONS WERE "SEVERE".

TABLE 59

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

	GROUP DESIGNATION:	II	IV	VI	VIII
	LESION GRADES	DOSE (mg/kg/day):	0	5	25	100
TISSUE/LESION	(P,1,2,3,4)	NUMBER IN GROUP:	12	12	12	12
DIGESTIVE SYSTEM						
LIVER			12	12	12	12
AGGREGATES, LYMPHOID, PERIPORTAL			2 (-,2,-,-,-)	2 (-,2,-,-,-)	1 (-,1,-,-,-)	-
CHOLANGIOFIBROSIS			-	-	-	1 (-,1,-,-,-)
FATTY CHANGE, MEDIAN CLEFT			2 (-,1,1,-,-)	2 (-,2,-,-,-)	1 (-,-,1,-,-)	1 (-,1,-,-,-)
HYPERTROPHY, HEPATOCYTE, CENTRILOBULAR			-	-	1 (-,1,-,-,-)	12 (-,5,7,-,-)
INFLAMMATION, SUBACUTE/CHRONIC			10 (,1, , ,) (-,0,-,-,-)	10 (,1, , ,) (-,0,-,-,-)	12 (,1, , ,) (-,2,-,-,-)	12 (,1, , ,) (-,2,-,-,-)
PANCREAS			12	0	0	12
AGGREGATES, LYMPHOID			3 (-,3,-,-,-)	-	-	1 (-,1,-,-,-)
TONGUE			12	0	0	11
ESOPHAGUS			12	0	0	12
DEGENERATION, MUSCULAR, FOCAL			1 (-,1,-,-,-)	-	-	-
INFLAMMATION, SUBACUTE/CHRONIC			2 (-,2,-,-,-)	-	-	1 (-,1,-,-,-)
STOMACH			12	0	1	12
EROSION/ULCER, GLANDULAR			-	-	1 (-,-,1,-,-)	-
DUODENUM			12	0	0	12
JEJUNUM			12	0	0	12
ILEUM			12	0	0	12
PEYER'S PATCH NOT PRESENT			1 (1,-,-,-,-)	-	-	2 (2,-,-,-,-)
PEYER'S PATCH NOT PRESENT (PRESENT ELSEWHERE)			1 (1,-,-,-,-)	-	-	1 (1,-,-,-,-)
CECUM			12	0	0	12
CELLULARITY INCREASED, LAMINA PROPRIA			3 (-,2,1,-,-)	-	-	3 (-,1,2,-,-)

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: II DOSE (mg/kg/day): 0 NUMBER IN GROUP: 12	IV 5 12	VI 25 12	VIII 100 12
DIGESTIVE SYSTEM (Cont'd)					
COLON		12	0	0	12
RECTUM		12	0	0	12
URINARY SYSTEM					
KIDNEYS		12	0	0	12
AGGREGATES, LYMPHOID		1 (-,1,-,-,-)	-	-	-
CYST		1 (-,1,-,-,-)	-	-	1 (-,1,-,-,-)
HYDRONEPHROSIS, BILATERAL		-	-	-	1 (-,1,-,-,-)
NEPHROPATHY, CHRONIC PROGRESSIVE		-	-	-	1 (-,1,-,-,-)
URINARY BLADDER		12	0	0	12
HYPERPLASIA, MUCOSAL		2 (-,2,-,-,-)	-	-	1 (-,1,-,-,-)
RESPIRATORY SYSTEM					
NOSE		12	0	0	12
PHARYNX/LARYNX		12	0	0	12
DEGENERATION, MUSCULAR, FOCAL		1 (-,1,-,-,-)	-	-	-
INFLAMMATION, MUSCULAR, FOCAL		1 (-,1,-,-,-)	-	-	-
INFLAMMATION, SUBACUTE/CHRONIC		-	-	-	1 (-,1,-,-,-)
TRACHEA		12	0	0	12
INFLAMMATION, SUBACUTE/CHRONIC		1 (-,1,-,-,-)	-	-	-

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	II	IV	VI	VIII
		DOSE (mg/kg/day):	0	5	25	100
		NUMBER IN GROUP:	12	12	12	12
RESPIRATORY SYSTEM (Cont'd)						
LUNGS			12	0	0	12
HEMORRHAGE			2	-	-	1
HISTIOCYTOSIS, ALVEOLAR			-	-	-	1
INFLAMMATION, ALVEOLAR			2	-	-	-
INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR			2	-	-	-
CARDIOVASCULAR SYSTEM						
HEART			12	0	0	12
DEGENERATION, MYOFIBER			1	-	-	-
AORTA			12	0	0	12
HEMATOPOIETIC SYSTEM						
BONE MARROW			12	0	0	12
THYMUS			12	0	0	12
HEMORRHAGE			5	-	-	6
SPLEEN			12	0	0	12
MANDIBULAR LYMPH NODE			12	0	0	12
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS			3	-	-	4
MEDIASTINAL LYMPH NODE			11	0	0	9
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS			10	-	-	8
MESENTERIC LYMPH NODE			12	0	0	12

TISSUE/LESION	II	IV	VI	VIII
RESPIRATORY SYSTEM (Cont'd)				
LUNGS				
HEMORRHAGE	(-,2,-,-,-)	-	-	(-,1,-,-,-)
HISTIOCYTOSIS, ALVEOLAR	-	-	-	(-,1,-,-,-)
INFLAMMATION, ALVEOLAR	(-,1,1,-,-)	-	-	-
INFLAMMATION, SUBACUTE/CHRONIC, PERIVASCULAR	(-,1,1,-,-)	-	-	-
CARDIOVASCULAR SYSTEM				
HEART				
DEGENERATION, MYOFIBER	(-,1,-,-,-)	-	-	-
AORTA				
HEMATOPOIETIC SYSTEM				
BONE MARROW				
THYMUS				
HEMORRHAGE	(-,5,-,-,-)	-	-	(-,5,1,-,-)
SPLEEN				
MANDIBULAR LYMPH NODE				
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS	(-,2,1,-,-)	-	-	(-,3,1,-,-)
MEDIASTINAL LYMPH NODE				
ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS, SINUS	(-,5,5,-,-)	-	-	(-,6,2,-,-)
MESENTERIC LYMPH NODE				

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	II	IV	VI	VIII
		DOSE (mg/kg/day):	0	5	25	100
		NUMBER IN GROUP:	12	12	12	12
ENDOCRINE SYSTEM						
PITUITARY GLAND			12	0	0	12
CYST			-	-	-	1 (-,-,1,-,-)
ADRENAL GLANDS			12	0	0	12
THYROID GLAND			12	12	12	12
ECTOPIC THYMUS TISSUE			1 (1,-,-,-,-)	-	-	1 (1,-,-,-,-)
HYPERTROPHY, FOLLICULAR CELL			-	-	2 (-,2,-,-,-)	9 (-,8,1,-,-)
PARATHYROID GLAND			10	0	0	12
NERVOUS SYSTEM						
BRAIN			12	0	0	12
SPINAL CORD			12	0	0	12
SCIATIC NERVE			12	0	0	12
EYES			12	0	0	12
EROSION/ULCER, CORNEAL			-	-	-	2 (-,1,1,-,-)
FOLD/ROSETTE, RETINAL			2 (-,2,-,-,-)	-	-	-
INFLAMMATION, EXTRAOCULAR (BLEEDING PROCEDURE)			3 (-,3,-,-,-)	-	-	4 (-,3,1,-,-)
LENS NOT PRESENT, UNILATERAL			1 (1,-,-,-,-)	-	-	1 (1,-,-,-,-)
OPTIC NERVE NOT PRESENT, BILATERAL			2 (2,-,-,-,-)	-	-	1 (1,-,-,-,-)
OPTIC NERVE NOT PRESENT, UNILATERAL			1 (1,-,-,-,-)	-	-	2 (2,-,-,-,-)

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	II	IV	VI	VIII
		DOSE (mg/kg/day):	0	5	25	100
		NUMBER IN GROUP:	12	12	12	12
MUSCULOSKELETAL SYSTEM						
FEMUR/KNEE JOINT			12	0	0	12
STERNUM			12	0	0	12
SKELETAL MUSCLE			12	0	0	12
INFLAMMATION, SUBACUTE/CHRONIC			-	-	-	1 (-,1,-,-,-)
REPRODUCTIVE SYSTEM						
OVARIES			12	0	0	12
UTERUS			12	0	0	12
CERVIX			12	0	0	12
VAGINA			12	0	0	12
ESTRUS STAGE: DIESTRUS			1 (1,-,-,-,-)	-	-	2 (2,-,-,-,-)
ESTRUS STAGE: ESTRUS			4 (4,-,-,-,-)	-	-	6 (6,-,-,-,-)
ESTRUS STAGE: METESTRUS			3 (3,-,-,-,-)	-	-	1 (1,-,-,-,-)
ESTRUS STAGE: PROESTRUS			4 (4,-,-,-,-)	-	-	3 (3,-,-,-,-)
INTEGUMENTARY SYSTEM						
SKIN			12	0	1	12
ALOPECIA DUE TO BARBERING			1 (1,-,-,-,-)	-	1 (1,-,-,-,-)	-
SALIVARY GLANDS			12	0	0	12
EXORBITAL LACRIMAL GLANDS			12	0	0	12
MAMMARY GLAND			10	0	0	8

TABLE 59 (Continued)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS – SUBCHRONIC ADULTS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	II	IV	VI	VIII
		DOSE (mg/kg/day):	0	5	25	100
		NUMBER IN GROUP:	12	12	12	12
MISCELLANEOUS						
OTHER			0	0	1	0
GROSS LESION (BONE FRACTURE) NOT AVAILABLE			-	-	1 (1,-,-,-,-)	-
CAUSE OF DEATH			12	0	0	12
SACRIFICED BY DESIGN			12	-	-	12
TOTAL ANIMALS WITH PRIMARY TUMORS			0	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS			0	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS			0	0	0	0

NOTES:
- THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
- LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. DOUBLE DIGIT NUMBERS ARE EXPRESSED VERTICALLY, FOR EXAMPLE: (,1, ,1,1) MEANS NO LESIONS (-,0,6,1,5) WERE GRADED "PRESENT", 10 LESIONS WERE "MINIMAL", 6 LESIONS WERE "MILD", 11 LESIONS WERE "MODERATE", AND 15 LESIONS WERE "SEVERE".

TABLE 60

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS - SATELLITE ADULTS

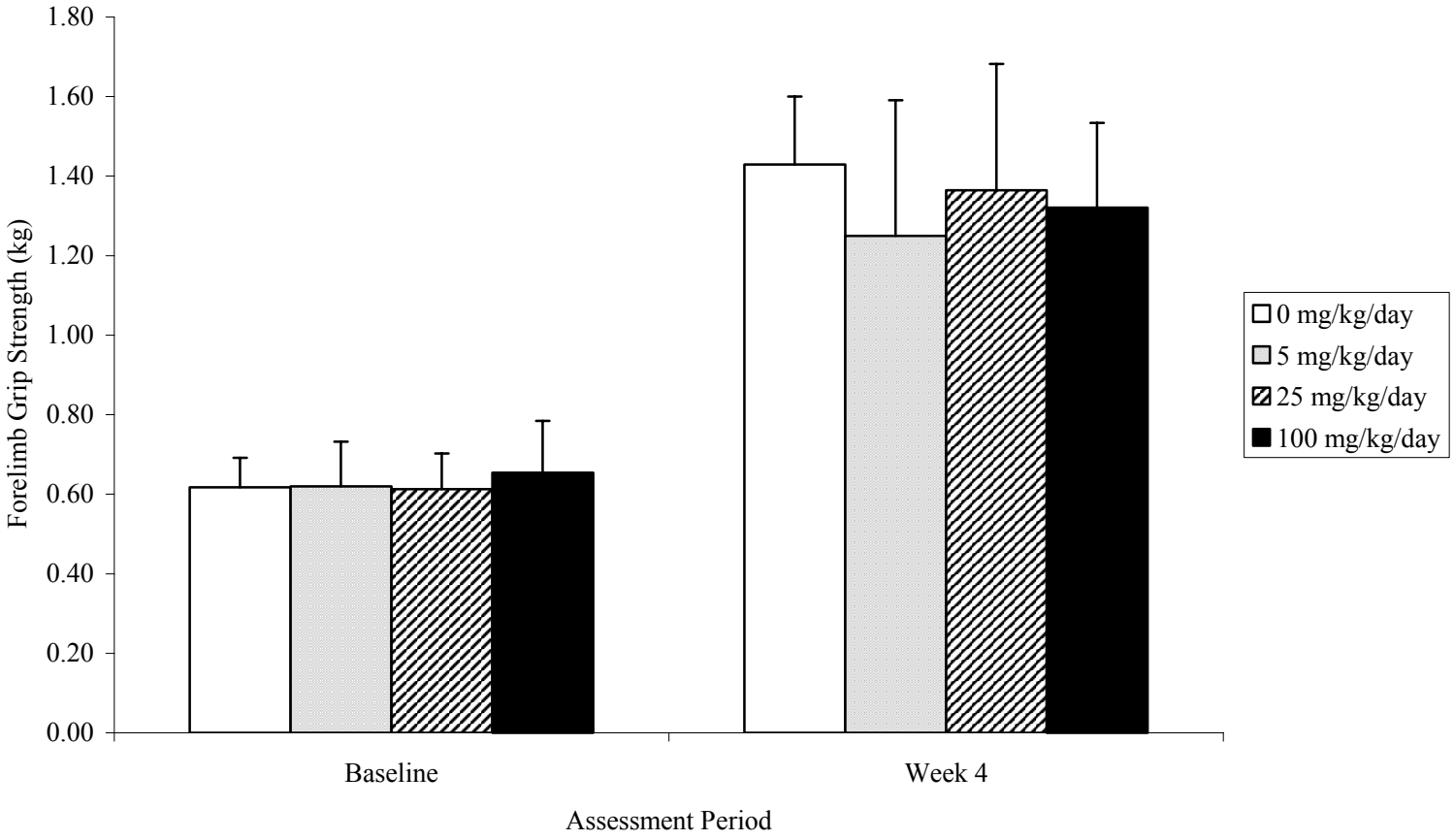
TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: / DOSE (mg/kg/day): / NUMBER IN GROUP:	II-0 0 12	IV-0 5 12	VI-0 25 12	VIII-0 100 12
REPRODUCTIVE SYSTEM						
OVARIES			2	0	1	2
UTERUS			2	0	1	2
ENDOMETRITIS (WITH BACTERIA)			-	-	-	1 (-,-,1,-,-)
CERVIX			2	0	1	2
VAGINA			2	0	1	2
ESTRUS STAGE: ESTRUS			1 (1,-,-,-,-)	-	-	-
ESTRUS STAGE: METESTRUS			1 (1,-,-,-,-)	-	-	1 (1,-,-,-,-)
ESTRUS STAGE: PROESTRUS			-	-	1 (1,-,-,-,-)	1 (1,-,-,-,-)
TOTAL ANIMALS WITH PRIMARY TUMORS			0	0	0	0
TOTAL ANIMALS WITH BENIGN TUMORS			0	0	0	0
TOTAL ANIMALS WITH MALIGNANT TUMORS			0	0	0	0

NOTES:
- THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
- LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. FOR EXAMPLE: (-,1,2,-,-) MEANS NO LESIONS WERE GRADED "PRESENT" (NON-GRADED LESIONS), 1 LESION WAS GRADED "MINIMAL", 2 LESIONS WERE GRADED "MILD", NO LESIONS WERE GRADED "MODERATE" AND NO LESIONS WERE GRADED "SEVERE".

FIGURES

FIGURE 1

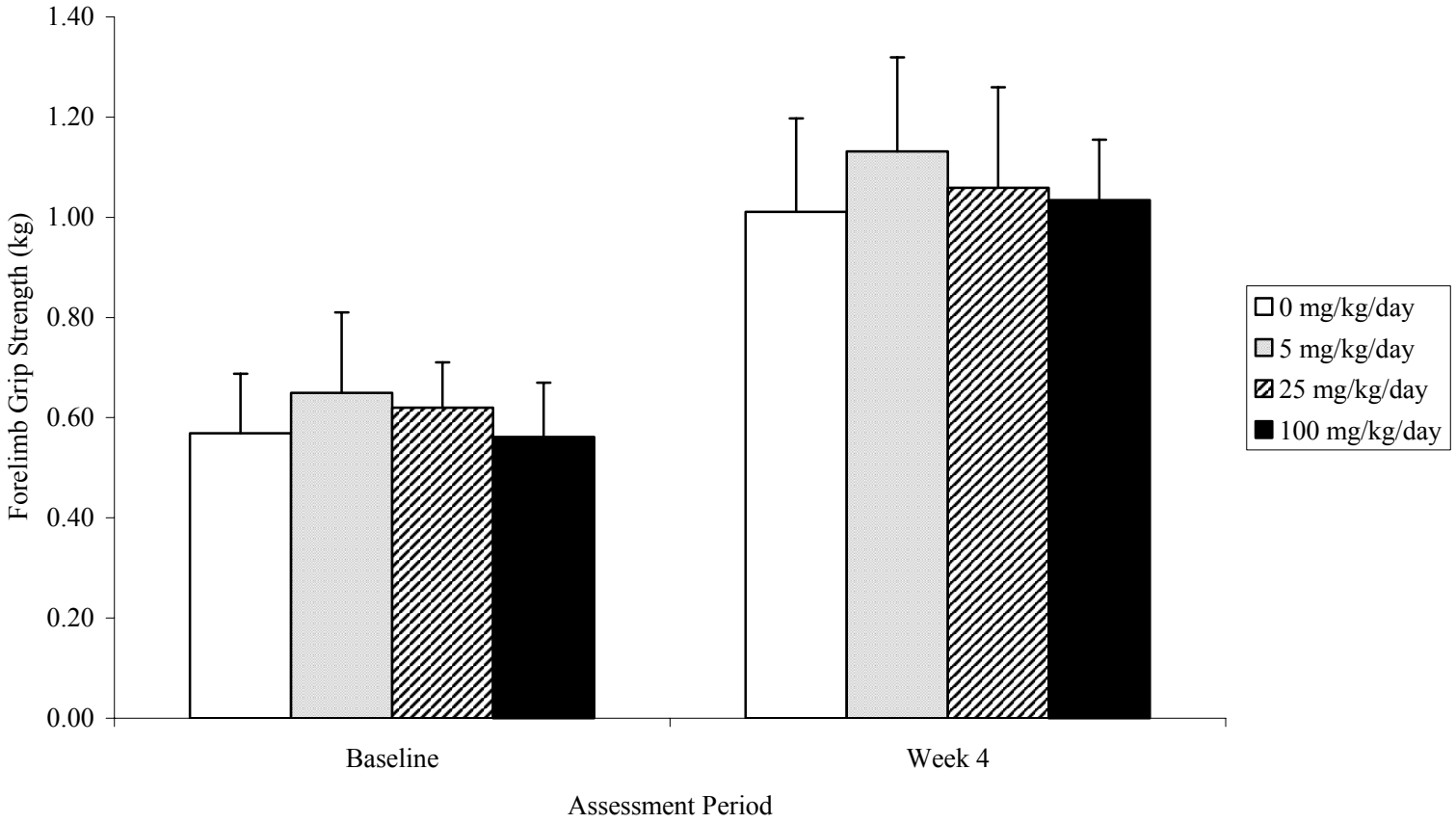
MEAN FORELIMB GRIP STRENGTH FOR MALE RATS



Error bars represent standard deviation.

FIGURE 2

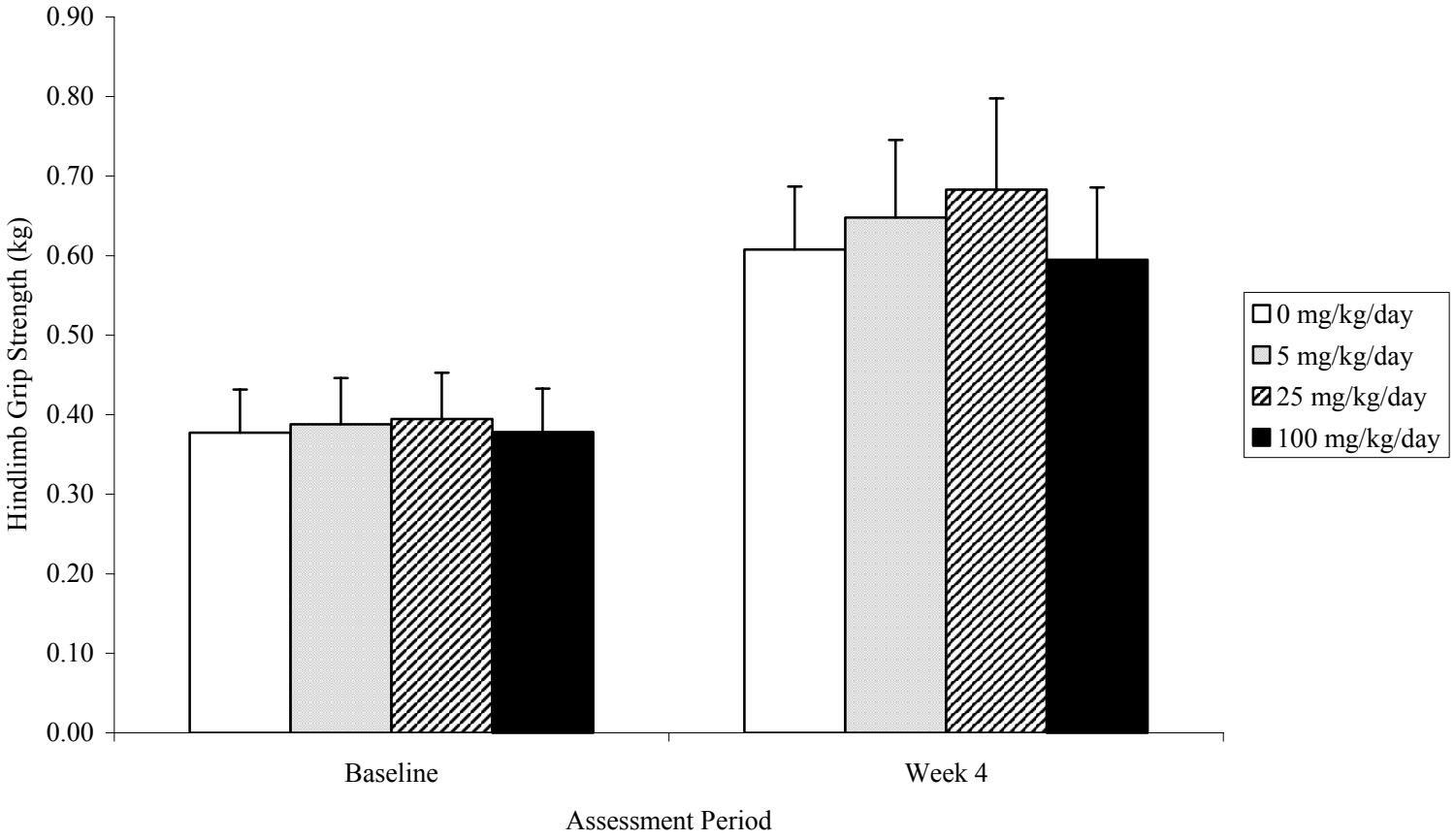
MEAN FORELIMB GRIP STRENGTH FOR FEMALE RATS



Error bars represent standard deviation.

FIGURE 3

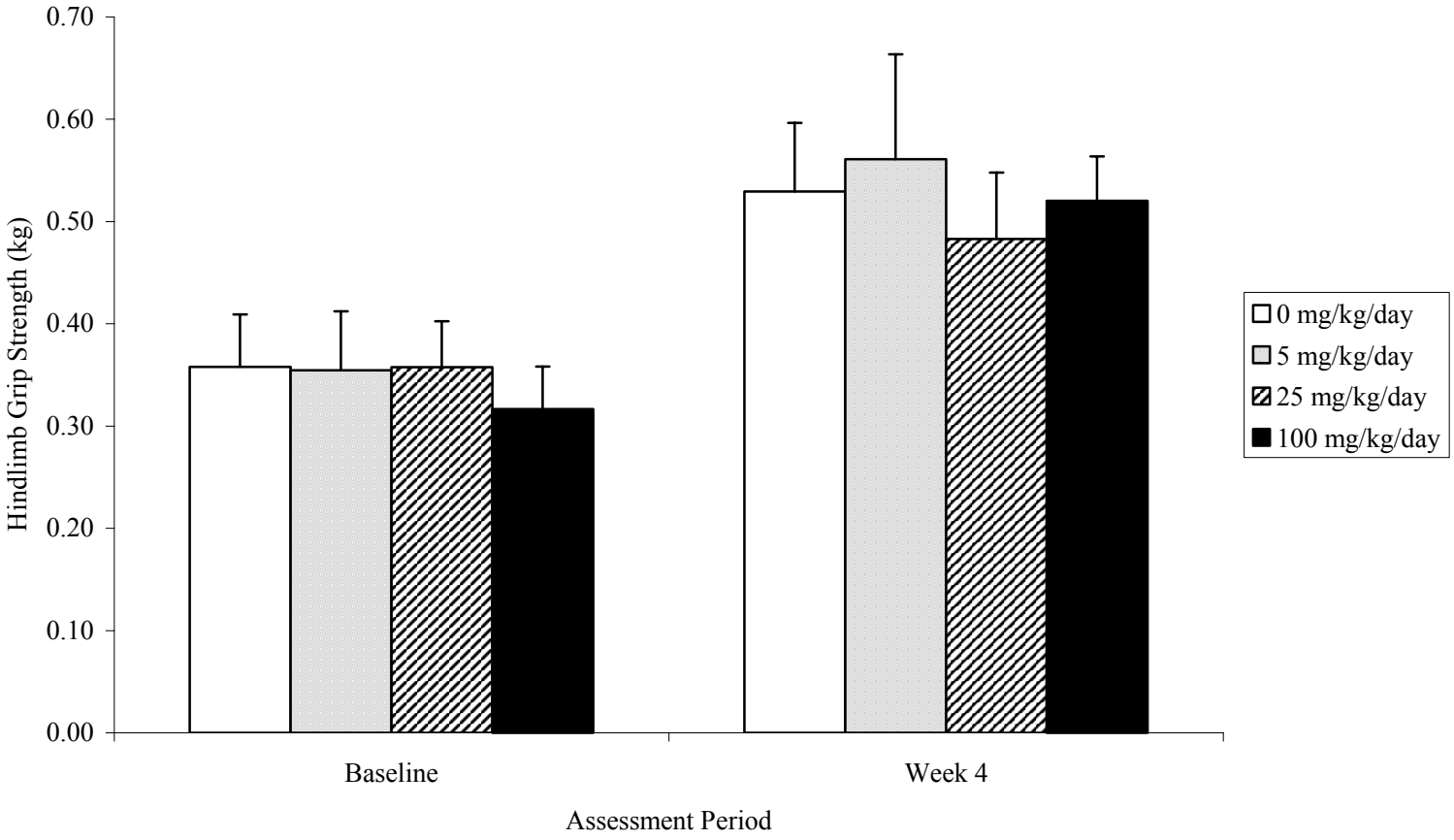
MEAN HINDLIMB GRIP STRENGTH FOR MALE RATS



Error bars represent standard deviation.

FIGURE 4

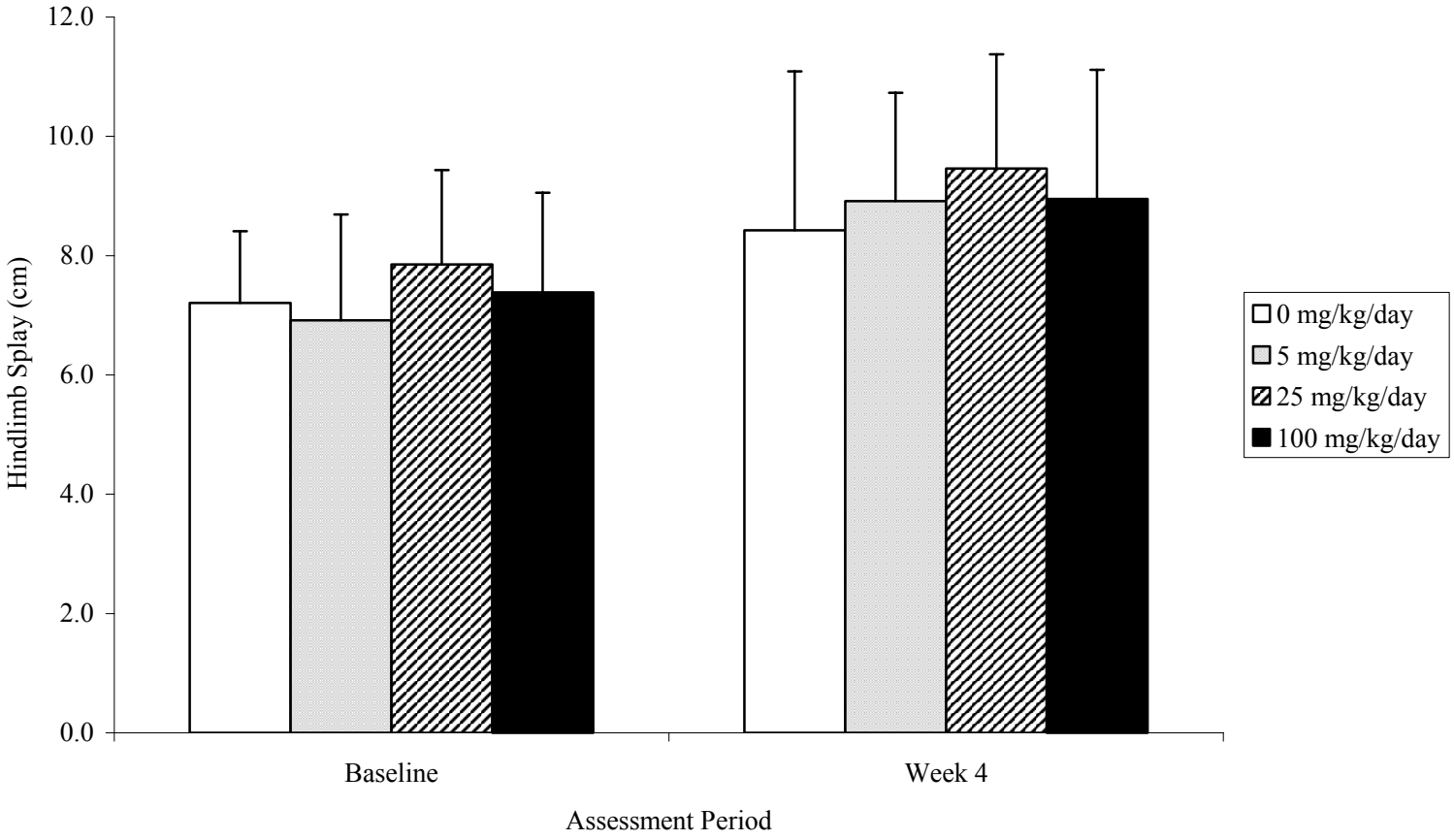
MEAN HINDLIMB GRIP STRENGTH FOR FEMALE RATS



Error bars represent standard deviation.

FIGURE 5

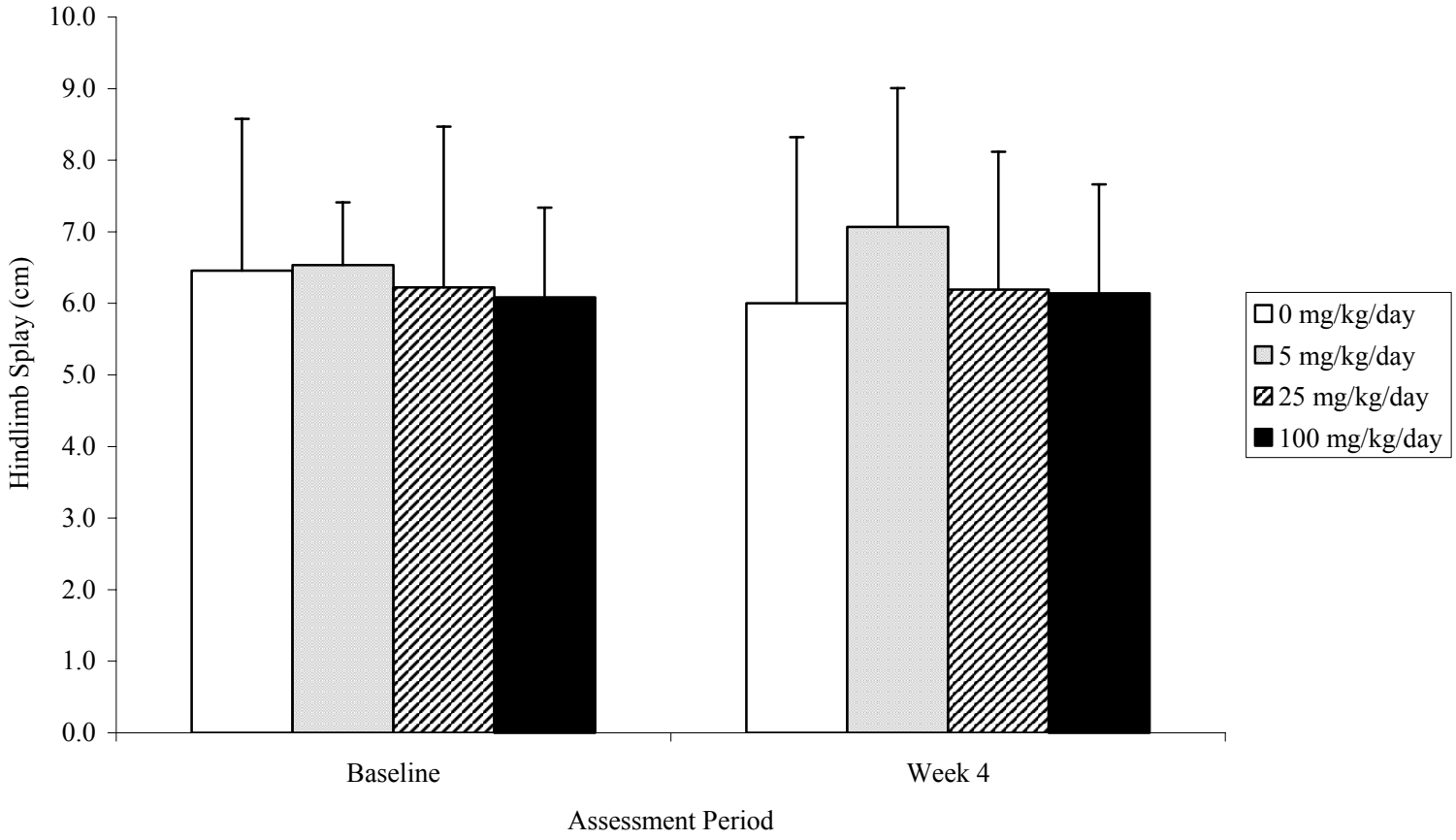
MEAN HINDLIMB SPLAY FOR MALE RATS



Error bars represent standard deviation.

FIGURE 6

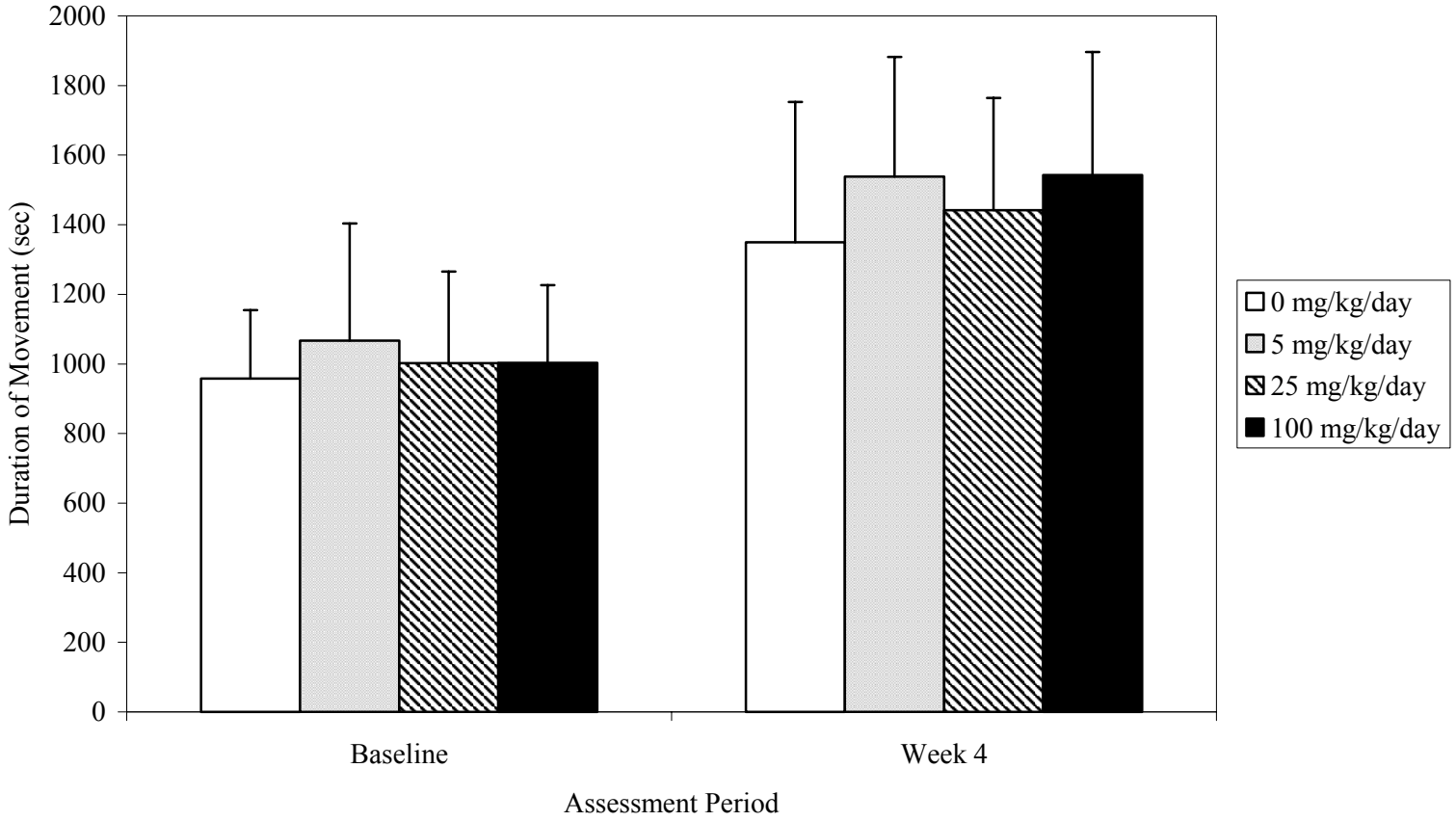
MEAN HINDLIMB SPLAY FOR FEMALE RATS



Error bars represent standard deviation.

FIGURE 7

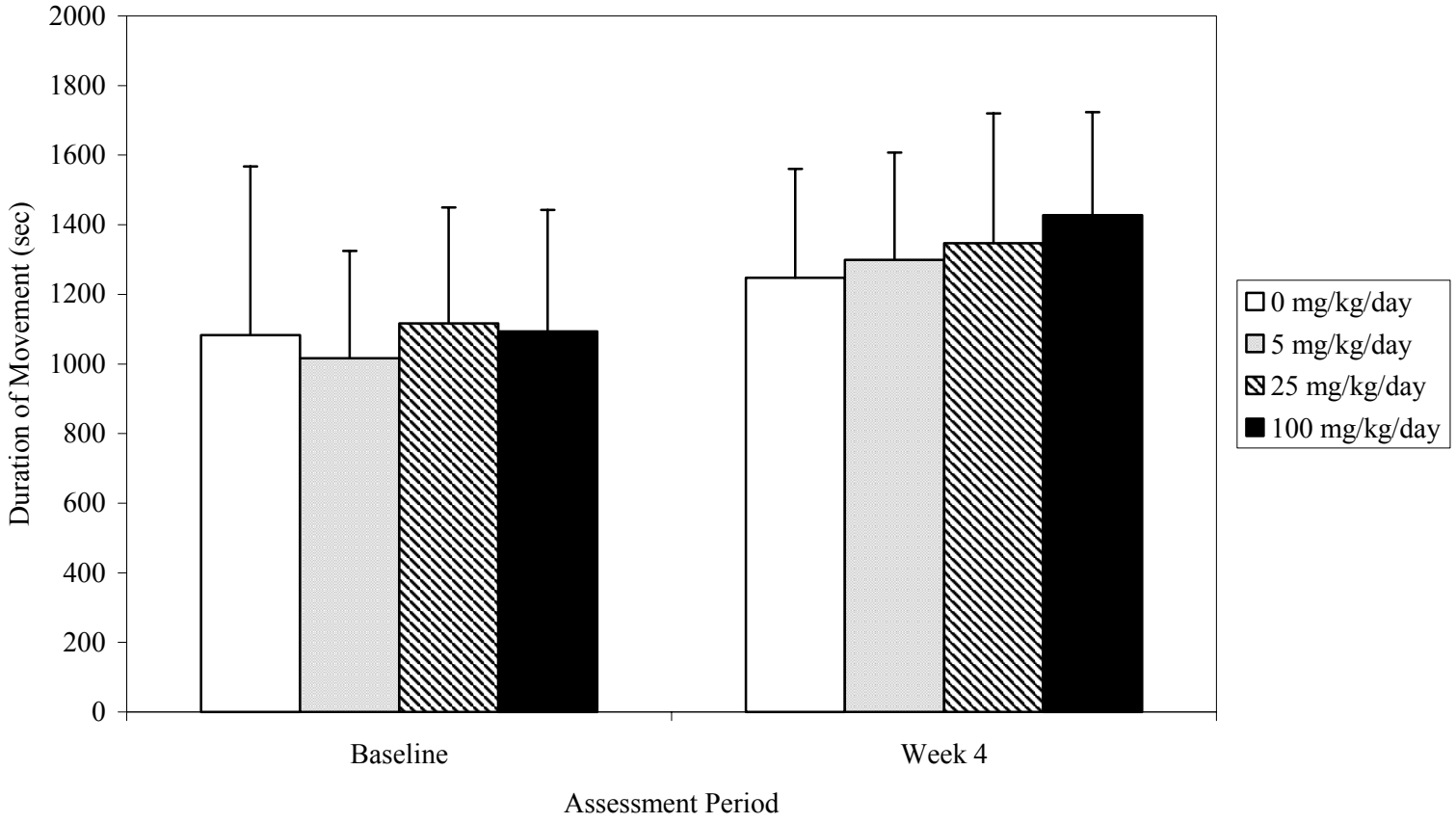
MOTOR ACTIVITY ASSESSMENT: MEAN TOTAL DURATION OF MOVEMENT FOR MALE RATS



Error bars represent standard deviation.

FIGURE 8

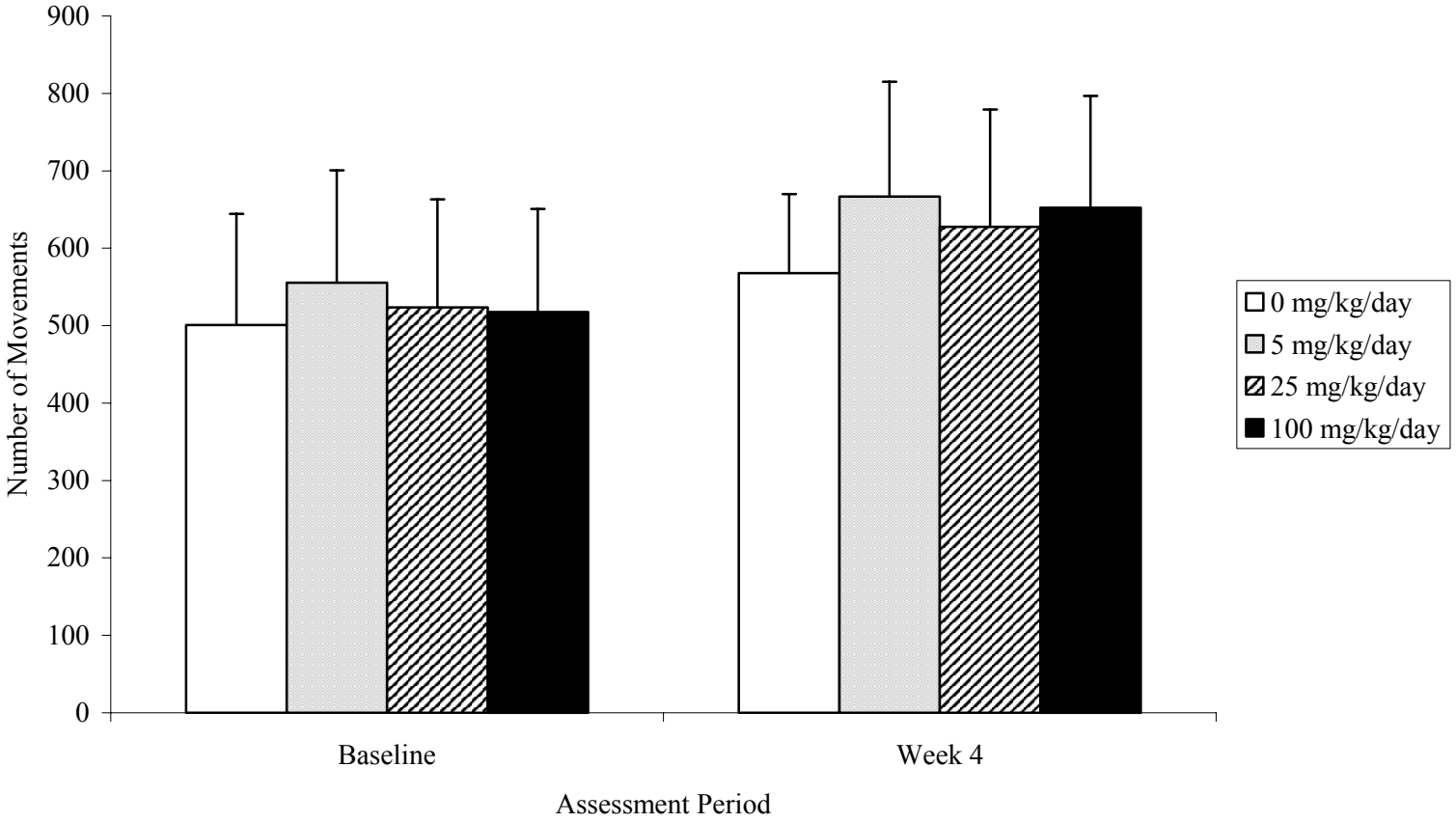
MOTOR ACTIVITY ASSESSMENT: MEAN TOTAL DURATION OF MOVEMENT FOR FEMALE RATS



Error bars represent standard deviation.

FIGURE 9

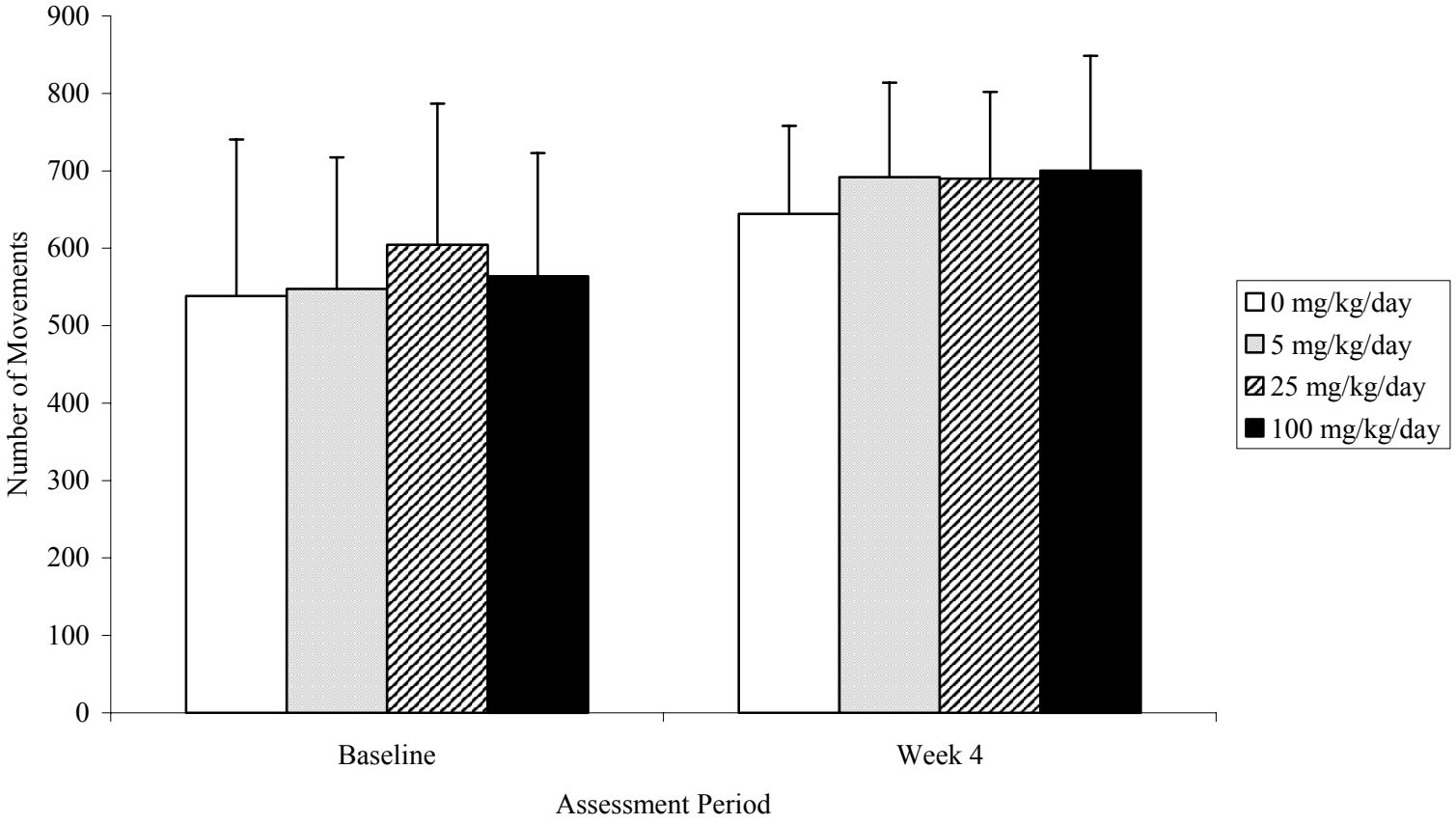
MOTOR ACTIVITY ASSESSMENT: MEAN TOTAL NUMBER OF MOVEMENTS FOR MALE RATS



Error bars represent standard deviation.

FIGURE 10

MOTOR ACTIVITY ASSESSMENT: MEAN TOTAL NUMBER OF MOVEMENTS FOR FEMALE RATS



Error bars represent standard deviation.

APPENDICES

APPENDIX A

Protocol and Protocol Amendments

Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats

Work Request Number 14294

Service Code 1422

Protocol

Haskell Animal Welfare Committee Number: DGRT-153GP
ACC Reference Number: OLF-92.0-HPV789-DHL

Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-12690

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Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-12690

INTRODUCTION AND PURPOSE

Dicyclopentadiene codimer (DCPD/codimer) will be evaluated for potential toxicity using a combined repeated dose toxicity/reproduction/developmental toxicity study. The purpose of this study is to evaluate the potential effects of DCPD/codimer when administered by gavage to male and female rats for a minimum of 28 consecutive days. General toxicity, clinical pathology, neurobehavioral activity, gross pathology, and histopathology will be evaluated.

In addition, a satellite group will be used to evaluate the potential effects of DCPD/codimer during premating (approximately 2 weeks), gestation (approximately 3 weeks), and lactation through day 4. In the satellite group, gonadal function, mating behavior, fertility, implantation, development of the conceptus, parturition, gross pathology, and histopathology will be evaluated.

Prior to conducting the main study, a range-finding study will be conducted in time-mated pregnant female rats. Dose levels for the main study will be selected based on the results of the range-finding study.

SPONSOR AND TEST FACILITY

The sponsor of this study is the American Chemistry Council, 1300 Wilson Boulevard, Arlington, Virginia 22209. Sponsor approval of the study protocol will be indicated by the signature of the sponsor's representative on the protocol.

The testing facility will be the DuPont Haskell Laboratory for Health and Environmental Sciences (1090 Elkton Road, Newark, Delaware 19714-0050) using Haskell Laboratory Standard Operating Procedures (SOPs) and animal facilities.

REGULATORY COMPLIANCE

Except as documented in the study records, the main study performed at Haskell Laboratory will be conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are consistent with the OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98)17.[1,2] The study design is based on Organisation for Economic Cooperation and Development (OECD), Guidelines for Testing of Chemicals, Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test, Guideline No. 422 (1996)[3] and the EPA Health Effects Guideline OPPTS 870.3650 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test.[4] Areas of noncompliance will be documented in the final report.

Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-12690

STUDY DESIGN

Treatment Groups and Dose Levels

Main Subchronic[a]				Satellite[b]		Dosage	
Group Male[a]	Number of Males	Group Female[a]	Number of Females	Group Females[b]	Number of Females	mg/kg/day	
I	12	II	12	II-0	12	0	(Control)
III	12	IV	12	IV-0	12	5	(Low)
V	12	VI	12	VI-0	12	25	(Medium)
VII	12	VIII	12	VIII-0	12	100	(High)

a Main study males and females (repeated-treatment, general toxicity and neurotoxicity endpoints)
b Satellite females (reproductive and developmental toxicity endpoints)

Study Parameters	Frequency
Clinical Observation • Predosing Observations (Main and Satellite)[a] • Postdosing Observations (Main and Satellite)[b] • Detailed Clinical Observations (Main)[c]	 • Daily prior to dosing • Daily following dosing (afternoon) • Pretest, and Days 8, 15, 22, and 29
Body Weight	• Study Days 1, 8, 15, 22, and 29 and at scheduled sacrifice (Main) • Days 1, 8, and 15 – Premating (Satellite) • Weekly – Mating (Satellite) • Daily - Gestation (Satellite) • Days 0 and 4 - Lactation (Satellite)
Food Consumption	• Study Days 1, 8, 15, 22 and 29 (Main) Food consumption will be discontinued for males upon cohabitation • Days 1, 8, and 15 – Premating (Satellite) • Days 0, 7, 14, and 21 - Gestation (Satellite) • Days 0 and 4 - Lactation (Satellite)
Functional Observational Battery (Main)	Pretest and Study Day 29-30
Motor Activity (Main)	Pretest and Study Day 29-30
Clinical Pathology (Main)	Study Day 30-31
Necropsy • Main Males • Main Females • Pregnant Satellite Rats • Satellite Rats that did not deliver a litter • Pups • Satellite Rats with no Evidence of Mating	Sacrifice Schedule • Study Day 30 • Study Day 31 • Lactation Day 4 • Gestation Day 27 (approximately) • Lactation Day 4 • Study Day 43 (approximately)

a Predosing Clinical Observations – Immediately prior to dosing, each rat will be individually handled and examined for abnormal behavior and appearance. Clinical abnormalities or No Abnormalities Detected (NAD) will be recorded in the study database for each rat prior to dosing.
b Postdosing Clinical Observations – All rats will be examined at cagesite in the afternoon after dosing. Clinical abnormalities only will be recorded in the study database.
c Detailed Clinical Observations will be recorded in the study database for all rats in the Main study, listing either clinical abnormalities or "NAD." During treatment, when these rats are scheduled for detailed clinical observation evaluations, detailed clinical observations evaluations will be performed and recorded first, predosing observations will then be performed and recorded, and the rats will then be dosed.

Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-12690

MATERIALS AND METHODS

A. Route of Administration

The test substance will be administered by oral intubation (gavage) to ensure maximal exposure and provide for comparison with other similar substances that have or will be tested by oral administration. The vehicle control substance will also be administered by oral gavage. The degree of the test substance or vehicle absorption by the test system is deemed beyond the scope and objectives of the study.

B. Duration of the Study

The start date of the study will be defined as the day the study protocol is signed by the Study Director. The experimental start date will be defined as the first day of dosing (test day 1). The experimental termination date of the main study will be defined as the final day of sacrifice at Haskell Laboratory. The completion date of the study will be defined as the date the final report is signed by the Study Director at Haskell Laboratory.

C. Test Substance

1. Identification:

Chemical Name:	Dicyclopentadiene/Codimer Concentrate
Other Name Used in this Protocol:	DCPD/codimer
CAS Registry Number:	68478-10-4
Haskell Sample Number:	25430
Lot Number:	120312
Purity:	100%
Color:	Pale straw colored
Form:	Liquid
Supplier for DCPD:	ExxonMobil
Vehicle:	Corn oil
Supplier for Corn Oil:	Mazola®
Lot Number for Corn Oil:	MZ-506300-LF-05

The test substance will be supplied as a liquid, stored below 70° F, and protected from light and air. Corn oil will be stored refrigerated.

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D. Test Substance Characterization

The test substance will be characterized by Haskell Laboratory's Analytical Group prior to the start of the study under a separate protocol.

1. Test Substance Stability

Stability of the test substance will be established by analyses at 2 time points. Aliquots will be taken after the end of the range-finding study, which will serve as the beginning of the study analysis for the main study. Aliquots will be taken again near the end of the current of study. The results of these analyses will be reported as test substance stability. The stability samples will be analyzed by gas chromatography using FID detection (see Appendix A). A peak of the major component will be compared to a standard to determine a ratio. A calibration curve will be prepared from this ratio, and the samples will be evaluated based on the calibration curve. The samples will be analyzed by Haskell Laboratory's Analytical Group on the day the samples are collected. Details regarding the analytical method used will be documented in the Analytical Chemistry Group study records.

E. Vehicle

Corn oil will be used as test substance vehicle. The corn oil will be purchased from reliable commercial vendors by Haskell Laboratory and is not expected to contain any contaminants that would interfere with the conduct of the study. The corn oil will be assumed to be stable under the conditions of the study.

F. Degree of Absorption

For the purposes of this study, clinical signs of toxicity and other manifestations of toxic effects will be considered to indicate uptake of the test substance. No attempt will be made to establish the actual systemic dose each rat received. All treatment-related effects will therefore be reported as a function of the administered dose(s).

G. Dosing Formulation Preparation and Sampling

Dosing formulations of the test substance will be prepared daily with corn oil by adding the corn oil to the measured amount of test material and stirring to establish uniformity. The method of preparing the dosing formulations will be documented in the study records.

Near the beginning of the study, 4 samples (approximately 3 mL) will be collected from each formulation, and will be analyzed for homogeneity/concentration verification, and 5-hour stability at room temperature. Near the middle and end of the dosing period, duplicate samples will be taken from all formulations and analyzed for concentration verification.

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The remaining formulation samples after dosing will be stored refrigerated, and discarded when the final results from the analysis have been accepted. Whenever samples are collected, a sample of the vehicle will also be collected and analyzed.

The samples will be mixed with chloroform and further diluted with hexane. The resulting solution will be analyzed by gas chromatography using FID detection. The samples will be analyzed by the Haskell Laboratory Analytical Group on the day the samples are collected. Details regarding the analytical method used will be documented in the Analytical Chemistry Group study records and the final report.

H. Test System

Approximately 56 male and 112 female Crl:CD®(SD)IGS BR rats (nulliparous) will be obtained from Charles River Laboratories, Inc (Raleigh, North Carolina). The rats will be approximately 8-10 weeks old at study start. This age corresponds to an estimated weight range of 200-325 g according to the vendor. Since the exact weight range for the animals in this study is not available prior to issuing the protocol, the exact weight range will be recorded in the raw data and stated in the final report. The Crl:CD®(SD)IGS BR rat has been selected on the bases of extensive experience with this strain at Haskell Laboratory and its suitability with respect to longevity, sensitivity, and low incidence of spontaneous diseases.

I. Animal Husbandry

1. Identification

Each rat will be assigned a unique 6-digit Haskell animal number and an individual cage identification number. The last 3 digits of the Haskell animal number will be tattooed on the tail of each rat. The Haskell animal number and cage identification number will both be included on the cage label.

2. Housing Environment

Rats will be housed singly in stainless steel, wire-mesh cages, suspended above cage boards, except as described in the next 2 paragraphs. Each cage rack will contain only rats of one gender.

During cohabitation, males designated for subchronic toxicity will be cohoused with the satellite females in their respective groups until evidence of copulation is observed.

Females in the satellite group will be housed in polycarbonate pans with bedding (Bed-o-Cobs®) from gestation day 19 or the end of the cohabitation period (if evidence of copulation was not detected) until sacrifice.

Animal rooms will be maintained at an acceptable temperature of 18°-26°C (targeted at 22°-24°C) and maintained at an acceptable relative humidity of 30%-70% (targeted at

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40%-60%). Animal rooms will be artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle.

3. Feed and Water

All rats will be provided tap water (United Water Delaware) *ad libitum*. They will be fed PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 (chunk chow) *ad libitum*.

4. Animal Health Monitoring

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore, and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian. Data are maintained separately from study records and may be included in the final report at the discretion of the study director.

J. Disposition of Moribund Animals or Animals Found Dead

During any portion of the main study, if a rat is determined to be moribund in the judgment of the Study Director, the consulting veterinarian, or their designee, the affected animal will be euthanized by CO_2 asphyxiation as soon as practical and will be subjected to a gross necropsy and tissue collection.

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K. Quarantine and Pretest Procedures

Upon arrival at Haskell Laboratory, all rats will be housed 1 per cage, sexes separate, in quarantine. The rats will be:

- quarantined for a minimum of 6 days.
- identified temporarily by cage identification.
- weighed at least 3 times during quarantine.
- observed with respect to weight gain and any gross signs of disease or injury during the entire pretest period (approximately 12 days).

The rats will be released from quarantine by the laboratory animal veterinarian or designee on the bases of acceptable body weights and clinical signs.

Rats that are accidentally killed or removed from study during the pretest period will be discarded without necropsy. Rats that are found dead or sacrificed *in extremis* during the pretest period will undergo a gross pathological examination to check for the presence of disease. Dependent upon these findings, further diagnostic procedures may be employed at the discretion of the study director, a pathologist, or the laboratory animal veterinarian. The results will not be reported in the final report unless considered significant to the evaluation of the study.

L. Assignment to Groups

Rats of each sex will be selected for use on study on the bases of adequate body weight gain and freedom from any clinical signs of disease or injury. They will be distributed by computerized, stratified randomization into study groups as designated in the Study Design, so that there are no statistically significant differences among group body weight means within a sex. To the extent possible, the weight variation on test day 1 will not exceed ± 20% of the mean for each sex.

After assignment to groups, each rat will be housed individually. At study start (test day 1) the rats will be approximately 8-10 weeks of age.

Rats that have not been assigned to a test group will be released for other laboratory purposes or be sacrificed by carbon dioxide asphyxiation and discarded without pathological evaluation, at the discretion of the study director.

M. Dose Selection

The dosages for the main study were determined from the range-finding study.

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N. Administration of Dosing Solutions

The test substance will be administered once daily by gavage at a dose volume of 2 mL/kg. Females designated for the subchronic toxicity study (main group) will be dosed for a minimum of 28 days. Females designated for the reproduction study (satellite group) will be dosed during the premating period (approximately 2 weeks), the mating period until evidence of copulation is observed (up to 2 weeks), the gestation period (approximately 3 weeks), and days 0-3 of lactation (if delivery is in progress at the time of dosing, the female will not be administered the dose). Females showing no evidence of copulation will continue to be dosed after the end of the cohabitation period until sacrifice. Males will be dosed during the premating period (approximately 2 weeks), during the mating period until evidence of copulation is observed, and subsequently until sacrifice (a minimum of 28 days total). Control rats will be dosed with corn oil (2 mL/kg) for a minimum of 28 days.

Dosages will be based on the most recently recorded weight.

O. Body Weights

1. Main Subchronic Study

All main study rats will be weighed on day 1, 8, 15, 22, and 29 and at scheduled sacrifice unless experimental findings or special scheduling situations warrant a change in the weighing schedule. In addition, rats undergoing functional observational battery and motor activity evaluations will be weighed on the days of those observations; however those weights will be included only in the appendix of the final report.

2. Satellite Study

Satellite female rats will be weighed according to the following schedule:

- Premating period – Days 1, 8, and 15
- Mating – Weekly
- Gestation – Daily
- Lactation – Days 0 and 4

P. Food Consumption and Food Efficiency

The amount of feed consumed by each rat over the weighing interval will be determined by weighing each feeder at the beginning of the interval and subtracting the diet remaining and the amount of spillage from the feeder at the end of the interval. From these determinations, mean daily feed consumption (g/day) will be calculated. Mean food efficiency will be calculated by dividing the amount of food consumed by the weight gain for a given interval of test days.

1. Main Subchronic Study

Feed consumption will be determined on day 1, 8, 15, 22, and 29 for each rat on the main study (food consumption in males will be discontinued upon cohabitation).

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2. Satellite Study

Satellite female rats will have feed consumption determined according to the following schedule:

- Premating period – Days 1, 8, and 15
- Gestation – Days 0, 7, 14, and 21
- Lactation – Days 0 and 4

Feed consumption will not be determined during cohabitation.

Q. Clinical Observations and Mortality

Clinical Observations will be determined throughout the test period for all rats. Moribund rats will be sacrificed and necropsied. Databases used for collection of clinical observation data will be documented in the study records.

1. Predosing Observations – Main Subchronic Study and Satellite Study

Immediately prior to dosing, each rat will be individually handled and examined for abnormal behavior and appearance. Clinical abnormalities or No Abnormalities Detected (NAD) will be recorded in the study database for each rat prior to dosing.

2. Postdosing Observations – Main Subchronic Study and Satellite Study

All rats will be examined at cagesite in the afternoon after dosing. Clinical abnormalities only will be recorded in the study database.

3. Detailed Clinical Observations – Main Subchronic Study

Rats in the Main Study will undergo a detailed clinical observation evaluation during pretest, and on Study Days 8, 15, 22, and 29. During the treatment period, when these rats are scheduled for detailed clinical observation evaluations, detailed clinical observations evaluations will be performed and recorded first, predosing observations will then be performed and recorded, and the rats will then be dosed.

Each rat will be individually handled and examined for abnormal behavior and appearance in a standardized arena. The detailed clinical observations will include (but are not limited to) evaluation of fur, skin, eyes, mucous membranes, occurrence of secretions and excretions, autonomic nervous system activity (lacrimation, piloerection, and unusual respiratory pattern), changes in gait, posture, response to handling, presence of clonic, tonic, stereotypical, or bizarre behavior. Clinical Observations will be recorded in the study database for all rats in the Main study, listing either clinical abnormalities or "NAD."

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R. Neurobehavioral Evaluations – Main Subchronic Study

For all the following assessments, the experimenter will be unaware of the group designation of the animal.

In order to accommodate the Neurotoxicology testing facility, the functional observational battery (FOB) and motor activity (MA) assessments will be conducted in 2 replicates per sex over a one-day period for baseline and a one-day period for the week 4 FOB. Replicate designations will not be reported in the final report, but will be recorded in the study records. Assignment to a given replicate will be counter balanced across all groups within a sex.

Prior to initiation of dosing, all rats designated for subchronic toxicity and approximately 8 extra rats per sex will be evaluated in the FOB test to establish their baseline FOB parameters. The FOB will be performed again on the rats designated for subchronic toxicity after a minimum of 28 days of treatment after initiation of test substance administration. During treatment, rats will be dosed after neurobehavioral evaluations are performed.

1. Functional Observational Battery (FOB)

FOB testing will consist of a series of quantified behavioral observations conducted in a sequence that proceeds from the least interactive to the most interactive.

During the FOB assessments, each rat will be evaluated in three "environments:" 1) inside the home cage; 2) upon removal from the home cage and while being handled; and 3) in a standard "open field" arena (approximately 85 x 59 x 20 cm). The animal's actual home cage is not amenable to transport between the housing room and neurobehavioral laboratory areas. Therefore, for the purposes of the FOB, the "home cage" is defined as the cage on the transport rack to which an individual animal is assigned and to which the rats have been acclimated and undisturbed for a period of at least 10 minutes.

For all of the following assessments, the experimenter will be unaware of the group designation of the animal.

Inside the home cage, the presence of the following will be recorded, if and when observed:

- palpebral closure
- writhing
- circling
- biting
- unusual changes in body posture
- gait/coordination

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During removal from the home cage and handling, each rat will be assessed for:

- fur appearance
- ease of removal
- ease of handling
- muscle tone
- the presence of
  - vocalizations
  - piloerection
  - bite marks
  - palpebral closure
  - lacrimation
  - exophthalmus
  - salivation

In the open field arena, the rats will be evaluated for

- unusual responses in
  - arousal
  - grooming
  - gait/coordination
  - posture
  - rate of respiration
  - ease of respiration
  - righting reflex
  - the number of rearing
- the presence of
  - convulsions
  - tremors
  - muscle fasciculation
  - muscle spasms
  - diarrhea
  - polyuria
  - palpebral closure
  - vocalizations

While in the standard arena, simple assessments of sensory function will be made, including:

- response to
  - approach/touch
  - auditory stimulus
  - tail pinch
  - the presence or absence of pupillary constriction assessed after a beam of light is directed into each eye.
  - pupillary constriction measured immediately prior to removing the rats from the motor activity chambers because the darkened room in which the apparatus is located facilitates observing the response.
  - the presence of diarrhea and polyuria on the cageboards below the motor activity cages will also be evaluated following each motor activity session.

The remainder of FOB testing involves standardized or calibrated devices. Fore- and hindlimb grip strength will be measured by a strain gauge device (Chatillon® -Digital Force gauge) (3 trials per animal per session). Hindlimb splay will be assessed by inking the hind paws and releasing the rat from a height of approximately 32 cm onto a piece of paper that covers a padded surface. Heel to heel distance will be measured from the inked impressions and recorded.

Rectal body temperature will be recorded with a YSI Precision™ 4000 Thermometer and temperature probe.

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2. Motor Activity (MA)

Motor activity sessions will be conducted on the same animals, the same day as FOB assessments, following the FOB assessments. Rats will be individually tested in one of 30 nominally identical, automated activity monitors (Coulbourn®). Groups will be counterbalanced across the monitors and time of day to the fullest extent possible. The infrared monitoring device enables measurement of two dependent variables, duration of movement and number of movements. A continuous movement is counted as one movement regardless of duration. Each test session will be 60 minutes in duration, and the results will be expressed for the total session, total motor activity over a 60-minute time period, as well as for 6 successive 10-minute blocks.

S. Clinical Pathology Evaluation

A clinical pathology evaluation will be conducted on all rats designated for subchronic toxicity at the time of scheduled sacrifice. These rats will be fasted overnight. Blood samples for hematology and clinical chemistry measurements will be collected from the orbital sinus of each animal while the animal is under light carbon dioxide anesthesia. Blood samples for coagulation parameters will be collected at sacrifice from the abdominal *vena cava* of each animal while the animal is under carbon dioxide anesthesia. Additional blood collected from the *vena cava* will be placed in a serum tube, processed to serum, and frozen at approximately -80°C. Serum may be used for additional testing as documented by protocol amendment, or will be discarded when the final report issues. Bone marrow smears will be prepared at the final sacrifice from all surviving animals and will be evaluated if warranted by experimental findings.

At the discretion of the study director or clinical pathologist, additional samples for selected clinical pathology tests may be collected from animals showing clinical evidence of toxicity or sacrificed *in extremis*.

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1. Hematology and Coagulation

Blood samples will be evaluated for quality by visual examination prior to analysis.

The following hematology and coagulation parameters will be determined:

red blood cell count
hemoglobin
hematocrit
mean corpuscular volume
mean corpuscular hemoglobin
mean corpuscular hemoglobin concentration
prothrombin time
activated partial thromboplastin time
red cell distribution width
absolute reticulocyte count
platelet count
white blood cell count
differential white blood cell count
microscopic blood smear examination

In addition, blood smears, stained with new methylene-blue, will be prepared from each animal undergoing a hematology evaluation and will be examined, if required, to substantiate or clarify the results of hematology findings.

2. Clinical Chemistry

The following clinical chemistry parameters will be determined:

aspartate aminotransferase
alanine aminotransferase
sorbitol dehydrogenase
alkaline phosphatase
total bilirubin
urea nitrogen
creatinine
cholesterol
triglycerides
glucose
total protein
albumin
globulin
calcium
inorganic phosphorus
sodium
potassium
chloride

T. Reproductive Assessment

1. Breeding

After 2 weeks of treatment with the test substance, each satellite female will be continually housed on a 1:1 basis with a randomly selected subchronic male of the same treatment level in the male's cage. On the day copulation is confirmed, the satellite female will be transferred back to individual cage housing. Mating pairs will be cohoused until evidence of copulation is observed (designated as day 0 of gestation), or until two weeks have elapsed. During the breeding period, daily vaginal lavage samples will be evaluated for the presence of sperm. The presence of a vaginal copulation plug *in situ* or sperm in vaginal lavage will be considered evidence of copulation.

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2. Gestation Procedures – Satellite Study

After they are transferred into polycarbonate pans (on day 19 of gestation (GD 19) for mated females, or at the end of the cohabitation period for females without evidence of copulation), female rats will be observed at least twice daily for signs of delivery and pups.

3. Lactation Procedures – Satellite Study

The day when delivery is complete is designated day 0 postpartum (LD 0). At each examination period, pups will be individually handled and examined for abnormal behavior and appearance; any dead, missing, or abnormal pups will be recorded. Any pups found dead or which are euthanized in moribund condition will be examined to the extent possible and discarded.

a. Day 0 Postpartum (Lactation Day 0)

Live and dead pups in each litter will be counted as soon as possible after delivery is completed. Live pups in each litter will be individually weighed and sex determined. Any clinical abnormalities in pups will be recorded.

b. Day 1 Postpartum (Lactation Day 1)

Pups in each litter will be counted by sex, individually weighed, and any clinical abnormalities in pups will be recorded.

c. Day 4 postpartum (Lactation Day 4)

Pups in each litter will be counted by sex and individually weighed. Any clinical abnormalities in pups will be recorded.

All offspring will be evaluated for external alterations, and euthanized by decapitation.

U. Anatomic Pathology Evaluation

1. Pretest

See Section K. Pretest Period.

2. Adult Rats

All rats found dead, accidentally killed, sacrificed *in extremis*, or sacrificed by design will undergo a gross evaluation and the tissues listed below will be collected. Rats will be euthanized by carbon dioxide asphyxiation and exsanguination. Rats in the Main Study only will be fasted after 3 p.m. on the afternoon before their scheduled sacrifice; rats in the Satellite Study will not be fasted before sacrifice. The order of sacrifice for scheduled deaths will be random among all treatment groups within a sex. Bone marrow smears will be prepared at the final sacrifice from all surviving animals and will be evaluated if warranted by experimental findings.

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The following tissues will be collected from rats that are found dead or accidentally killed (tissue integrity permitting), sacrificed *in extremis*, or sacrificed by design including satellite females.

Digestive System	Hematopoietic System	Reproductive System
liver	spleen	Male
esophagus	thymus	testes
stomach	mediastinal lymph node	epididymides
duodenum	mandibular lymph node	prostate
jejunum	mesenteric lymph node	seminal vesicles
Ileum (including Peyer's patches	bone marrow[a]	coagulating glands
cecum		Female
colon	Endocrine System	ovaries (with oviducts)
rectum	pituitary gland	cervix
tongue	parathyroid gland	uterus[b]
pancreas	thyroid gland	vagina
Urinary System	adrenal glands	
kidneys		Integumentary System
urinary bladder	Nervous System	skin
	brain (three sections)	salivary glands
Respiratory System	spinal cord (three levels)	lacrimal glands
lungs	Eyes (with optic nerve)	Mammary gland (females only)
trachea	sciatic nerve	
nose		Miscellaneous
Pharynx/larynx		gross observations[c]
	Musculoskeletal System	
Cardiovascular System	femur/knee joint	
heart	sternum	
aorta	Skeletal muscle	

a Bone marrow will be collected with the femur and sternum.

b The uteri of females in the satellite groups will be examined for the presence and number of implantation sites and corpora lutea.

c Gross observations made at necropsy for which histopathology is not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) will generally not be collected.

All tissues will be placed in the appropriate fixative.

For rats in the Main subchronic study that are sacrificed by design, the following organs will be weighed: liver, kidneys, lungs, adrenal glands, thymus, spleen, brain, heart, and testes and epididymides and/or ovaries and uterus. For rats in the Satellite study, the brain, the following organs will be weighed and trimmed: liver, kidney, lungs, ovaries and uterus. Relative organ weights (percent of final body weight; ratio to brain weight) will be calculated. Final body weights determined just prior to necropsy will be used in the assessment of organ weight changes. Organs from rats found dead, sacrificed *in extremis,* or accidentally killed may be weighed at the discretion of the pathologist or study director.

Histologic examination of all the tissues in the table above will be conducted on rats designated for subchronic toxicity from the high-treatment and control group animals. Examination of

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tissues from the remaining groups will be limited to relevant gross lesions and those tissues that demonstrate treatment-related histologic effects in the high-treatment group.

Gross lesions and tissues listed from satellite females will be collected and saved for possible future histopathology. The uteri of all mated females will be examined for the number of implantation sites and corpora lutea. The uteri of mated females that did not deliver litters will be visually examined for corpora lutea and implantation sites in order to verify pregnancy status. In the event that histopathology is considered necessary for satellite females that deliver a litter, it will be addressed in a protocol amendment. All preserved reproductive tissues from animals with impaired reproductive performance (e.g., failure to mate, conceive, sire, deliver healthy offspring, or nurse) will be examined microscopically.

Paraffin embedded tissues will be sectioned approximately 5-6 microns thick, stained with hematoxylin and eosin, and examined microscopically by a veterinary pathologist. Selected gross observations for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, tail chronic dermatitis, calculus, and deformities of the teeth, toe, tail, or ear pinna) will be saved, but will generally not be processed for microscopic evaluation. Rats found dead or sacrificed *in extremis* will be histologically examined in a similar manner in an attempt to determine cause of death or morbidity.

Additional procedures to identify and/or clarify histologic features of lesions may be performed at the discretion of the pathologist and will be documented in the final report.

3. Pups

All offspring surviving to postnatal day 4 will be evaluated for external alterations and euthanized by decapitation. Pups found dead or which are euthanized in moribund condition will be examined to the extent possible and discarded.

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DATA ANALYSES

The following table lists the indices of reproductive function that will be calculated for the P_1 adults.

Reproductive Function Calculations

Mating Index (%)	=	Number Copulated[a] / Number Cohabited	x 100
Fertility Index (%)	=	Number Pregnant[b] / Number Copulated[a]	x 100
Gestation Index (%)	=	Number of Litters with at Least One Live Pup / Number of Litters	x 100
Implantation Efficiency (%)[c]	=	Number of Pups Born / Number of Implantation Sites	x 100
Pups Born Alive (%)c	=	Number of Pups Born Alive / Number of Pups Born	x 100
Viability Index (%)[c,d]	=	Number of Pups Alive Day 4 Preculling / Number of pups born alive	x 100
Preimplantation Loss	=	Number of Corpora Lutea / Number of Implantation Sites	x 100
Postimplantion Loss	=	Number of Implantation Sites / Number of Pups	x 100

a Evidence of copulation = intravaginal copulatory plug, found dead pregnant, or delivery of a litter.
b Including those found dead pregnant during gestation.
c To be determined for each litter. Mean and standard deviation for each dose level will be calculated.
d Excluding litters sacrificed due to death of dam during lactation.

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Statistical Methods

	Method of Statistical Analysis		
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Gestation Length Implantation Site Numbers Implantation Efficiency Mean Number of Pups Per Litter Percent Born Alive Viability Index 0-4 Day Viability Number of Corpora Lutea Organ Weight	Test for lack of trend[5]	Sequential application[6] of the Jonckheere-Terpstra trend test[7]	Preliminary tests for pairwise comparison
	OR[a]		
	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	One-way analysis of variance[10] and Dunnett's test[11]	Kruskall-Wallis test[12] and Dunn's test[13]
Food Efficiency	None	One-way analysis of variance[10] and Dunnett's test[11]	
Incidence of Clinical Observations Incidence of Descriptive Functional Observational Battery Parameters Mating Index Fertility Index Gestation Index	None	Cochran-Armitage test for trend[10][c]	
Grip Strength Foot Splay Body Temperature	Bartlett's test[14] for homogeneity of variances	One-way analysis of variance[10] and Dunnett's test[11]	Kruskall-Wallis test[12] and Dunn's test[13]
Motor Activity[d]	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	Repeated measures analysis of variance followed by contrasts[15]	Sequential application[6] of the Jonckheere-Terpstra trend test[7]
Clinical Pathology[e]	Levene's test for homogeneity[8] and Shapiro-Wilk test[9] for normality[b]	One-way analysis of variance[10] followed with Dunnett's test[11]	Kruskal-Wallis test[12] followed with Dunn's test[13]
Mean Pup Weights (Covariates: litter size, sex ratio) Sex Ratio	None	Linear contrast of least squares means[16]	Dunn's test[13]

a Pairwise comparisons and associated preliminary tests are only conducted if the test for lack of trend is significant.

b If the Shapiro-Wilk test is not significant but Levene's test is significant, a robust version of Dunnett's test will be used.

c If the incidence is not significant, but a significant lack of fit occurs, then Fisher's Exact test[17] with a Bonferroni correction is used.

d Test day and 10-minute intervals will be used as repeated-measure factors.

e When an individual observation is recorded as being less than a certain value, calculations are performed on half the recorded value. For example, if bilirubin is reported as <0.1, 0.05 is used for any calculations performed with that bilirubin data.

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For each parameter analyzed with a trend test, the test will be applied to the data sequentially. If a significant dose-response is detected, data from the top dose group will be excluded and the test repeated until no significant trend is detected.[6] For litter parameters, the proportion of affected fetuses per litter or the litter mean will be used as the experimental unit for statistical evaluation.[18] The level of significance selected is $p < 0.05$. Additional statistical tests will be used, and other parameters analyzed, if deemed necessary.

Where the data are tied and the standard large sample version of Jonckheere's test[7] is not applicable, exact p values will be calculated using permutation methodology.[19]

SPECIAL SAFETY AND HANDLING PROCEDURES

The test substance will be dispensed, mixed, and sampled in a chemical fume hood. Laboratory personnel will wear Racal respirators while mixing, dosing, and sampling the test material or the formulations containing the test material.

HUMANE TREATMENT OF ANIMALS

In so far as is consistent with the scientific objectives of the study, experiments and procedures performed by Haskell Laboratory personnel have been designed to minimize pain and distress inflicted upon the experimental animals. If the animals appear in pain, distress, or become moribund, laboratory guidelines will apply. Haskell Laboratory SOPs will apply for animals found dead or *in extremis*. Guidelines concerning the humane treatment of animals are reviewed and maintained by the Haskell Animal Welfare Committee (HAWC).

RECORDS AND SAMPLE STORAGE

All original records will be retained at Haskell Laboratory, E. I. du Pont de Nemours and Company, Newark, Delaware or at Iron Mountain Records Management, 200 Todds Lane, Wilmington, Delaware. Preserved wet tissues, paraffin blocks, histological slides, blood smears and bone marrow smears will be retained at Haskell Laboratory. A sample of the test substance will be collected for archive purposes and retained at Haskell Laboratory.

CHANGES IN THE PROTOCOL

Changes in the protocol will be documented in protocol amendments signed by the Study Director and Sponsor's representative.

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FINAL REPORT

A final report will be written and will be reviewed by the Haskell Quality Assurance Unit (prior to sponsor review). The report will include but is not limited to:

- a GLP compliance statement
- detailed information about the test substance
- analytical report(s)
- vehicle control
- test system and animal husbandry
- protocol and amendments

The study results will include:

- body weights/weight gain
- food consumption/food efficiency
- clinical signs of toxicity
- reproduction, gestation, and lactation parameters
- neurobehavioral evaluations - functional observational battery and motor activity
- clinical pathology
- pathology
- a discussion of study results
- conclusions
- robust summary

A draft of the Haskell Laboratory final report will be submitted to the American Chemistry Council prior to finalization of the report.

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PROTOCOL APPENDIX A

METHOD FOR THE ANALYSIS OF DICYCLOPENTADIENE/CODIMER CONCENTRATE IN DOSING FORMULATIONS

A. Recovery Sample Analysis

Concurrent with dosing formulation analyses, recovery of DCPD/Codimer concentrate from spiked Mazola corn oil will be tested at the low level, at the mid level and at the high level to confirm the analytical method. DCPD/Codimer concentrate will be weighed in an appropriate amount for each level and diluted with 3 mL of Mazola® corn oil. All recovery samples were then mixed for dispersion of the DCPD/Codimer concentrate in the corn oil. The samples will then be processed and analyzed in the same manner as the dosing samples at similar concentrations.

B. Dosing Formulation Treatment

Each dosing sample (3 mL) will be mixed with 10 mL chloroform to dissolve the Mazola® corn oil then diluted to 100 mL with hexane and mixed to dissolve the DCPD/Codimer concentrate in the suspension. The dosing samples will be analyzed without further dilution or will be further diluted with hexane to an expected concentration of active ingredient prior to analysis. Before all final dilutions, the internal standard (refer to Calibration and Quantitation Section) at the appropriate concentration previously determined and the 0 mg/mL sample (initial dilution) will be added to each test sample to give an equivalent final concentration of the matrix (corn oil diluted with chloroform/hexane) and internal standard in all samples.

C. Chromatographic Conditions

Instrument:	Hewlett-Packard Model 6890 GC
Column:	DB-1, 30 m x 0.25 mm ID, 0.25 µm film thickness
Injector:	Split, 180°C
Detector:	FID; 250°C
Carrier Gas:	Helium (2.7 mL/min)
Split vent:	26.9 mL/min
Injection Volume:	3 microliter
Oven Program:	Gradient
Initial Temperature:	50°C
Initial Time:	1.0 min.
Level 1 Rate:	20°C/min.
Level 1 Temperature:	250°C
Level 1 Time:	2.00 min.
Total run time:	13.00 min.

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D. Calibration and Quantitation

A separate sample of the test substance, DCPD/Codimer concentrate, will be used as the analytical reference standard for the analysis. A stock solution will be prepared in hexane. Calibration solutions will be prepared in hexane from this solution to bracket the diluted sample concentration in the analysis. A stock solution of the internal standard (toluene, 99.5% pure) will be prepared in hexane and added to each calibration standard and test solution to give a final concentration needed for the analysis. Before all final dilutions, the 0 mg/mL sample (initial dilution) was added to each solution to give an equivalent final concentration of the matrix (corn oil diluted with chloroform/hexane) in all standards. The ratio of the peak heights for DCPD isomer #2 and for the internal standard from replicate GC analysis of these solutions will be used to construct a calibration curve by least squares regression. Measured concentrations for the samples will be determined by applying the peak height ratios from replicate injections of each sample to the calibration curve.

Test substance homogeneity/uniformity in the vehicle will be evaluated by calculating the coefficient of variation (C.V. = standard deviation/mean x 100) of the measured concentrations in the top, middle, and bottom samples (homogeneity) or duplicate samples (concentration verification) for each dosing level. A coefficient of variation of less than or equal to 10% is the standard criterion at Haskell Laboratory for acceptable distribution of the test substance throughout the solution.

The mean result of the homogeneity samples or concentration verification duplicate samples for each dosing level will be used to determine the concentration of the test substance for the respective dosing levels.

Stability will be evaluated by using the mean result of the homogeneity samples as the baseline for comparing the corresponding stability results.

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PROTOCOL APPENDIX B

STUDY FUNCTIONS AND STUDY PERSONNEL

Study Function	Study Personnel
Study Director:	Linda A. Malley Senior Research Toxicologist
Analytical Chemistry Evaluation:	Janet Maslanka Analytical Chemist
Neurobehavior Evaluation:	Linda A. Malley Neurotoxicologist
Clinical Pathology Evaluation:	Nancy E. Everds Clinical Pathologist
Anatomic Pathology Evaluation:	Greg Sykes, V.M.D. Veterinary Pathologist

Study Dates	
Baseline FOB/MA	April 3-4, 2003
Baseline Detailed Clinical Observations	April 7, 2003
Initiation of test substance administration	April 9, 2003
Co-house males with satellite females	April 23, 2003
Week 4 FOB/MA	May 7-8, 2003
Clinical pathology	May 8-9, 2003
Sacrifice of main study males and females	May 8-9, 2003
Start sacrifice for repro satellite females and females with no pups	May 19, 2003 (Approximately)
Audited draft report to sponsor	November 11, 2003

Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-12690

SIGNATURES

Approved by: Linda A. Malley 26-March-2003

Linda A. Malley, Ph.D.
Study Director
Developmental, Reproductive, and Neurobehavioral Toxicology
DuPont Haskell Laboratory

Date

Elizabeth Moran, Ph.D.
Sponsor Representative

April 14 2003
Date

cc:

J.M. Lewis	M.K. Vaillancourt	K.B. Brebner
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D.L. Tyler	D.M. Hoban	J.W. Green
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N.P. Betts	S.W. Records	M. Wilford
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Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-12690

Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats

Work Request Number 14294
Service Code 1422
American Chemistry Council Reference Number: OLF-92.0-HPV789-DHL

PROTOCOL AMENDMENT 1

The protocol is amended as follows:

1. Page 5, Section C., Test Substance Identification, change the test substance lot number to "121302", change the color to "colorless liquid", and change the Lot Number for Corn Oil to "Same as expiration date".

Rationale: The lot number of the test substance, the color of the test substance, and the lot number for the corn oil were incorrect in the original protocol. The manufacturer of the corn oil uses the expiration date as the lot number.

2. Page 5, Section C., Test Substance Identification, change the last paragraph to: "The test substance will be supplied as a liquid, stored at or below 70° F, and protected from light and air."

Rationale: According to information supplied by the sponsor, the test substance should be at or below 70° F.

3. Page 10, Section P. Food Consumption and Food Efficiency, last sentence, change to: " Mean food efficiency will be calculated by dividing the body weight gain by the amount of food consumed for a given interval of test days."

Rationale: The change corrects the calculation of food efficiency in the original protocol.

4. Page 11, Section R, Neurobehavioral Evaluations – Main Subchronic Study, second paragraph, first sentence, change to: "In order to accommodate the Neurotoxicology testing facility, the functional observational battery (FOB) and motor activity (MA) assessments will be conducted in 2 replicates per sex over a two-day period for the baseline and week 4 FOB. "

Rationale: The sentence was corrected to be consistent with study schedules.

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Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats

Work Request Number 14294
Service Code 1422
American Chemistry Council Reference Number: OLF-92.0-HPV789-DHL

PROTOCOL AMENDMENT 1 (Continued)

5. Page 17, Section U.2. Adult Rats, delete Peyer's patches from the ileum and add them as a foot note to the "Digestive System". Footnote "b", change to "Females in the satellite groups were examined for the presence and number of uterine implantation sites and ovarian *corpora lutea*.

Rationale: The Peyer's patches occur in several locations throughout the digestive system. Corpora lutea are located in the ovary.

6. Page 19, Data Analyses, change "pre-implantation loss" to the number of implantation sites subtracted from the number of corpora lutea. The resulting difference will be divided by the number of implantation sites. Change "post-implantation loss" to the number of pups subtracted from the number of implantation sites. The resulting difference will be divided by the number of implantation sites. Add the following calculation for sex ratio: The number of male pups born/litter divided by the number of pups born per litter.

Rationale: The equations for calculation of pre-implantation loss and post-implantation loss were incorrect in the protocol, and were corrected. The equation for sex ratio was added to the protocol for clarification.

7. Page 21, Records and Sample Storage, delete the last line of the paragraph.

Rationale: Due to the potential for peroxide formation during long-term storage, a sample of the test substance will not be archived.

Approved by: Linda A. Malley 30-Jan-04
Linda A. Malley, Ph.D. Date
Study Director
Developmental, Reproductive, and Neurobehavioral Toxicology
DuPont Haskell Laboratory

2/11/04
Elizabeth Moran, Ph.D. Date
Sponsor Representative

Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats DuPont-12690

Dicyclopentadiene/Codimer Concentrate: Combined Repeated Dose Toxicity Study and Reproductive/Developmental Toxicity Screening Test in Rats
Work Request Number 14294
Service Code Number 1422
PROTOCOL AMENDMENT 2

The protocol is amended as follows:

1. P. 19-21, Data Analyses, replace with the following:

Data Analyses

1. Reproductive Function Calculations

The following table lists the indices of reproductive functions that were calculated for the P_1 adults.

Mating Index (%)	=	$\frac{\text{Number Copulated}^a}{\text{Number Cohabited}}$	x 100
Fertility Index (%)	=	$\frac{\text{Number Pregnant}^b}{\text{Number Copulated}^a}$	x 100
Gestation Index (%)	=	$\frac{\text{Number of Litters with at Least One Live Pup}}{\text{Number of Litters}}$	x 100
Implantation Efficiency (%)[c]	=	$\frac{\text{Number of Pups Born}}{\text{Number of Implantation Sites}}$	x 100
Pups Born Alive (%)[c]	=	$\frac{\text{Number of Pups Born Alive}}{\text{Number of Pups Born}}$	x 100
Viability Index (%)[c,d]	=	$\frac{\text{Number of Pups Alive Day 4 Preculling}}{\text{Number of pups born alive}}$	x 100
Preimplantation Loss[e]	=	$\frac{\text{Number of } \textit{corpora lutea} - \text{Number of implantation sites}}{\text{Number of } \textit{corpora lutea}}$	
Postimplantation Loss[e]	=	$\frac{\text{Number of implantation sites} - \text{Number of pups}}{\text{Number of implantation sites}}$	

a Evidence of copulation = intravaginal or cageboard copulatory plug and/or sperm in vaginal lavage sample, found dead pregnant, or delivery of a litter.
b Including those found dead pregnant during gestation.
c Determined for each litter. Mean and standard deviation for each dose level were calculated.
d Excluding litters sacrificed due to death of dam during lactation.
e Restricted to pregnant dams.

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2. Summary Data for Body Weight, Weight Gain, Food Consumption, and Food Efficiency

Body weight data for subchronic males, subchronic females, and satellite females were summarized weekly. Body weight gain, food consumption, and food efficiency data for subchronic males were summarized over weekly intervals, and for the intervals of days 1-15, 15-29, and 1-29 so that any potential effects from cohabitation on these parameters could be evaluated. Body weight gain, food consumption, and food efficiency data for subchronic females and satellite females were summarized over weekly intervals and for test days 1-29 (subchronic females), test days 1-15 of premating (satellite females), test days 0-21 of gestation (satellite females), and test days 0-4 of lactation (satellite females).

3. Statistical Methods

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Gestation Length Implantation Site Numbers Implantation Efficiency	Test for lack of trend	Sequential application of the Jonckheere-Terpstra trend test	Preliminary tests for pairwise comparison
	OR[a]		
Mean Number of Pups per Litter Percent Born Alive 0-4 Day Viability Viability Index Number of *Corpora Lutea* Sex Ratio Pre-implantation Loss Post-implantation Loss Organ Weights	Levene's test for homogeneity and Shapiro-Wilk test for normality[b]	One-way analysis of variance followed with Dunnett's test	Kruskal-Wallis test followed with Dunn's test
Food Efficiency	None	One-way analysis of variance followed with Dunnett's test	
Incidence of Clinical Observations Incidence of FOB Descriptive Parameters Mating Index Fertility Index Gestation Index	None	Cochran-Armitage test for trend	
Clinical Pathology[d]	Levene's test for homogeneity and Shapiro-Wilk test for normality[b]	One-way analysis of variance followed with Dunnett's test	Kruskal-Wallis test followed with Dunn's test

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		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Mean Pup Weights (Covariates: litter size, sex ratio)	None	Linear contrast of the least square means	None

a Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.
b If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed with Dunn's test.
c If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test with a Bonferroni correction was used.
d When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that data. When an individual observation was recorded as being greater than a certain value, calculations were performed on the recorded value. For example, if specific gravity was reported as >1.083, 1.083 was used for any calculations performed with that data.

a. Statistical Analysis of Motor Activity

Motor activity (number and duration of movements) is done by repeated measures ANOVA with day and bin (epoch) as repeated factors, with bin nested within day, possibly after a normalizing, variance stabilizing transformation. Since bin has more than two levels, consideration must be given to the variance-covariance structure in testing for significance of treatment effects overall or within a single day or bin. Where the correlations between observations on the same subject in different bins on the same day appear to vary as separation in time increases (a real possibility), either a Huynh-Feldt or Greenhouse-Geisser adjustment is made or an alternative variance-covariance structure (e.g., unstructured, auto-regressive, heterogeneous auto-regressive, or heterogeneous compound symmetry) is used that reflects this varying correlation. Assessment of the need for such an adjustment or alternative variance-covariance structure can be done using Mauchly's criterion for sphericity, through inspection of the sample variance-covariance matrix, or through the use of variance-covariance diagnostics described in Hocking *et al.*, Green and Hocking, Grynovicki and Green, and Searle *et al.*.

The responses are assessed for normality using the Shapiro-Wilk test applied to the residuals from the ANOVA model and appropriate plots. If the data are judged non-normal, then a normalizing transformation is sought. If no such transformation can be found, then separate analyses for the responses from each day and bin are done. If no normality problem is found or is resolved by a transformation, then Levene's test for variance homogeneity is done. If significant variance heterogeneity is found from this test and appropriate plots, then a Low normalizing, variance-stabilizing transformation is sought. If none is found, then separate analyses for the responses from each day and bin are done.

In the context of this repeated measures ANOVA, linear contrasts are estimated to determine treatment effects. A linear contrast for dose trend is estimated as are individual comparisons of treatments to control. This is done on each day, averaging across bins, and in each bin. To control the false positive rate associated with these comparisons, adjustments to the p-values are

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made based on the significance (or lack thereof) of the Dose-by-Day and Dose-by-Day-by-Bin interactions, and the test for linear trend in the dose-response.

In addition, a repeated measures analysis is done of the daily sums over bins of the responses from each animal. Such sums (or, equivalently so far as conclusions are concerned, averages) are more likely to be normally distributed than are the individual responses, so that separate analyses by each time point are less likely. These data are analyzed by the same method described below for grip strength.

b. Statistical Analysis of Grip Strength, Foot Splay, Body Temperature, and Rearing

These endpoints are analyzed by repeated measures ANOVA with day as the only repeated factors, possibly after a normalizing, variance stabilizing transformation. Since day has only two levels, the Greenhouse-Geisser conditions are automatically satisfied and no special treatment of the variance-covariance matrix or the tests for treatment effects is needed. Normality and variance homogeneity are evaluated as above, analogous actions are taken where significant non-normality or variance heterogeneity is encountered, and tests for treatment effects are conducted as above, except that bin is not a consideration.

c. Trend Test

For each parameter analyzed with a trend test, the test was applied to the data sequentially. If a significant dose-response was detected, data from the top dose group was excluded and the test repeated until no significant trend was detected.

d. Litter Parameters

For litter parameters, the proportion of affected fetuses per litter or the litter mean was used as the experimental unit for statistical evaluation.

e. Level of Significance

The level of significance selected was $p < 0.05$ for trend tests Levene's, Shapiro-Wilk, Kruskal-Wallis, Dunn's, and linear contrasts. Where the data were tied and the standard large sample version of Jonckheere's test was not applicable, exact p values were calculated using permutation methodology.

Rationale: At the request of the sponsor, the Data Analyses section was expanded and rewritten to provide additional details for analysis of the data. In addition, the denominators for pre-implantation loss and post-implantation loss were corrected.

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2. Page 21, Records and Sample Storage, remove the last sentence pertaining to an archive sample of the test substance.

Rationale: The test substance has the potential to form peroxides which can be an explosive hazard. Therefore, an archive sample cannot be retained, and the container must be discarded safely.

3. Page 22, References, change reference #3 to: OECD Guideline for Testing of Chemicals. Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. (422) (1996).

Rationale: The reference in the original protocol was incorrect.

4. Protocol Amendment #1, Item #4, change "Page 11" to "Page 12."

Rationale: A typographical error was made in the page number of item #4 in amendment #1, which was corrected.

Approved by: _____ _____

Linda A. Malley, Ph.D. Date
Study Director
Developmental, Reproductive, and Neurobehavioral Toxicology
DuPont Haskell Laboratory

_____ _____

Elizabeth Moran, Ph.D. Date
Sponsor Representative

cc: Haskell

APPENDIX B

Test Substance Characterization

APPENDIX B

Explanatory Notes

The test substance characterization appendix contains the following components:

1. Characterization of DCPD/Codimer Concentrate - study report
2. Appendix 1 of the study report – Study Protocol
3. Appendix 1 of the Study Protocol – Analytical method for DCPD/Codimer Concentrate analysis provided by the sponsor
4. Appendix 2 of the study report – Study protocol amendments
5. Appendix 3 of the study report – Certificate of analyses of reference substances

STUDY TITLE: **Characterization of Dicyclopentadiene/Codimer Concentrate (DCPD/Codimer Concentrate)**

STUDY DIRECTOR: Vladimir Capka, Ph.D.
Research Chemist

REPORT COMPLETED ON: September 29, 2003

TESTING FACILITY: DuPont Haskell Laboratory for Health and Environmental Sciences
1090 Elkton Rd.
Newark, Delaware 19714

STUDY SPONSOR: American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

PROJECT IDENTIFICATION: American Chemistry Council Reference Number:
OLF-92.0-HPV789-DHL

DuPont Study Number: DuPont-11642
Work Request Number: 14294
Study Code Number: 378

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in accordance with U.S. EPA Good Laboratory Practice Standards (GLPs) of TSCA 40 CFR Part 792, which are consistent with OECD Principle of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98)17.

Reference substances were not characterized under Good Laboratory Practice Standards; however, they were obtained from reliable sources (dicyclopentadiene, Aldrich, Milwaukee, WI; 3a, 4, 7, 7a-tetrahydroindene, TCI America, Portland, OR).

Vladimir Capka

29-Sep-2003

Vladimir Capka, Ph.D.
Study Director
DuPont Haskell Laboratory for Health and Environmental Sciences

Date

Elizabeth J. Moran

16-Sept-2003

Elizabeth J. Moran, Ph.D
Sponsor Representative
American Chemistry Council

Date

QUALITY ASSURANCE DOCUMENTATION

Haskell Sample Number(s):

25430

Dates of Inspections:

Protocol: February 21, 2003

Conduct: February 21, 2003

Records, Reports: May 12, 2003

Dates Findings Reported to:

Study Director: February 21, 2003; May 12, 2003

Management: February 21, 2003; May 13, 2003

Reported by: Joseph C Hamill 29-Sep-2003
Joseph C. Hamill
Staff Quality Assurance Auditor
Date

STUDY PERSONNEL

Protocol, Analysis, and Report by: Vladimir Capka, Ph.D., Study Director

STUDY DATES

Study Initiation Date:	January 29, 2003
Experimental Start Date:	February 19, 2003
Experimental Termination Date:	March 03, 2003
Study Completion Date:	May 12, 2003

CERTIFICATION OF AUTHENTICITY

This report, for Haskell Laboratory Study Number DuPont – 11642, provides accurate and complete evaluation of the raw data obtained from this study.

Vladimir Capka, Ph.D., Research Chemist
Study Director
DuPont Haskell Laboratory for Health and Environmental Sciences

29-Sep-2003
Date

S. Mark Kennedy, Ph.D.
Manager, Analytical Chemistry
DuPont Haskell Laboratory for Health and Environmental Sciences

29-Sep-2003
Date

TABLE OF CONTENTS

1. SUMMARY

Characterization of DCPD/Codimer Concentrate test substance was performed by Gas Chromatography (GC) with Flame-Ionization Detection (FID). The composition of the test substance was determined as follows:

Component	**Composition (%)**
3a, 4, 7, 7a-Tetrahydroindene	2.67 ± 0.04
Dicyclopentadiene[a]	30.8 ± 0.2
Unidentified Components Above 0.1%	65.2
Other Unidentified Components Below 0.1%	1.60

[a] Based on sum of isomers

2. INTRODUCTION

This report details the results of characterization of DCPD/Codimer Concentrate test substance. The characterization was performed by GC/FID based on the method provided by the Sponsor.

3. TEST SUBSTANCE

DCPD/Codimer Concentrate test substance was supplied by the Sponsor. The test substance was identified by the Sponsor as a complex hydrocarbon of variable composition.

Test Substance Name: DCPD/Codimer Concentrate (CAS Number: 68478-10-4)
CA Index Name: Naphtha (petroleum), light steam-cracked, debenzenized, C8-16-cycloalkadiene concentrate
Lot Number: 121302
Haskell Laboratory Number: 25430
Purity: not applicable (100% of the stream)
Date Received: December 18, 2002
Expiration Date: June 13, 2003
Test substance was stored at or under 70°F under nitrogen atmosphere until dispensed.

Test substance composition provided by the Sponsor:

29.175 wt % endo- and exo-DCPD[a]
18.726 wt % C4-MCPD[b] and C5-MCPD codimers
13.210 wt % MCPD dimer
12.903 wt % CPD[c]-MCPD codimer
8.129 wt % C8 aliphatic and aromatic hydrocarbons
7.144 wt % C4-CPD and C5-CPD codimers
3.625 wt % MCPD-C7 dimer
2.771 wt % Tetrahydroindene

1.917 wt % Trimers
0.927 wt % C7 cyclic hydrocarbons
0.697 wt % C5 acyclic hydrocarbon dimer
0.634 wt % MCPD monomer
0.078 wt % CPD monomer
0.063 wt % C6 acyclic hydrocarbons

[a] DCPD stands for dicyclopentadiene.
[b] MCPD stands for methylcyclopentadiene.
[c] CPD stands for cyclopentadiene.

4. REFERENCE SUBSTANCES

The following reference substances were used in the study for the purpose of identification of the test substance components:

- Dicyclopentadiene, CAS Number: 77-73-6
  Supplier: Aldrich, Milwaukee, WI
  Lot Number: 14209PI
  Purity: 99.7 % (as a mixture of exo- and endo- isomers)
  Expiration Date: October 30, 2007 (assigned by Haskell Laboratory)
  Haskell Laboratory Identification Number: 22703-246

- 3a, 4, 7, 7a-Tetrahydroindene, CAS Number: 3048-65-5
  Supplier: TCI America, Portland, OR
  Lot Number: GK01
  Purity: 99.0 %
  Expiration Date: December 1, 2006 (assigned by Haskell Laboratory)
  Haskell Laboratory Identification Number: 22703-248

5. EXPERIMENTAL METHODS, PROCEDURES, AND RESULTS

The method used for test substance characterization using Gas Chromatography with Flame Ionization Detection (GC/FID) is summarized below:

Instrument:	Hewlett Packard HP6890 gas chromatograph with 7683 autosampler
GC Column:	DB-1, J&W, 50 m length, 0.25 mm internal diameter, 0.25 µm film thickness
Carrier Gas:	Helium
Injector Temperature:	180°C
Pressure:	17.6 psi
Split Ratio:	100:1
Wash Solvent A:	hexane
Wash Solvent B:	chloroform
Syringe Size:	5 µL
Injection Volume:	0.1 µL

Carrier Gas Flow Rate:	1.4 mL/min, constant flow mode
Initial Temperature:	-10°C, increase at 2°C/min to Final Temperature 1
Final Temperature 1:	20°C, increase at 10°C/min to Final Temperature 2
Final Temperature 2:	250°C, hold at Final Temperature 2 for 2 minutes
Run Time:	40 min
Detector:	Flame Ionization Detector (FID)
Detector Temperature:	280°C
Hydrogen Flow:	40 mL/min
Air Flow:	450 mL/min
Makeup Gas Type:	Helium

Reference compounds were diluted with chloroform prior to GC analysis. 3a, 4, 7, 7a-tetrahydroindene was injected as a 78 mg/g solution, and dicyclopentadiene as a 137 mg/g solution, respectively, and then compared with chromatograms of blank chloroform to identify solvent-related peaks in the reference compound chromatograms. The test substance was analyzed without any prior dilution. All reference substance solutions, and chloroform, as well as the test substance were analyzed in triplicate. Averages of all applicable area % and retention time values were calculated. Identity of the test substance components was determined by comparing the GC retention times of the test substance components with those of the reference substances. Peaks in all resulting chromatograms were electronically integrated and the area % was obtained using the following calculation

$$area\%_i = \frac{area_i}{\sum_{i=1}^{n} area_i} \times 100\%$$

where n is the number of integrated chromatographic peaks in the test substance chromatogram, $area_i$ and $area\%_i$ are the chromatographic peak area and the area % of the i-th component, respectively.
Test substance composition with respect to the commercially available reference substances is summarized in Table I. Comprehensive test substance composition is summarized in Table II.
Typical chromatograms of DCPD/Codimer Concentrate test substance, Reference standard solutions, and the chloroform solvent are in Figures 1 – 4.
Based on the agreement between the test substance composition provided by the Sponsor and the composition obtained from this study, we believe that the intended test substance was received by Haskell Laboratory.

6. RETENTION OF DATA

At the completion of the study, all original raw data, protocol, and a copy of the final report will be archived by Haskell Laboratory for period of ten (10) years. After the ten-year period, all study-specific raw data will be transferred to the Sponsor unless instructed otherwise. Haskell Laboratory will also maintain all facility-specific raw data, such as, but not limited to, instrument logs and personnel training records.

Characterization of DCPD/Codimer Concentrate

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Table I

DCPD/Codimer Concentrate test substance composition with respect to the commercially available reference substances

	THI[a] (%)	DCPD[b] isomer 1 (%)	DCPD[b] isomer 2 (%)	DCPD[b] (sum of isomers)[d] (%)
Run 1	2.65	2.19	28.5	30.66
Run 2	2.63	2.20	28.6	30.75
Run 3	2.71	2.22	28.7	30.96
Average[c]	2.67 ± 0.04			30.8 ± 0.2

Unidentified Components Higher than 0.1 %: 65.2 %
Other Unidentified Components Below 0.1 %: 1.60 %

[a] THI stands for 3a, 4, 7, 7a-tetrahydroindene
[b] DCPD stands for dicyclopentadiene
[c] Average was calculated based on exact area % of individual runs and then rounded as dictated by scientific significance of the corresponding standard deviation.
[d] Sum of isomers calculated based on exact area % values of individual isomers and then rounded.

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Table II

Composition of DCPD/Codimer Concentrate test substance. Components are listed based on their retention time.

Average Retention Time[a] (min)	Average Area %[a, b]	Standard Deviation[a, b]	Component Identification[b]
8.46[c]	0.064[c]	0.004[c]	< 0.1%
14.86	0.35	0.02	unidentified
15.17	0.27	0.01	unidentified
20.04	0.104	0.006	unidentified
20.07	0.199	0.009	unidentified
20.22	0.137	0.007	unidentified
20.57[d]	0.056[d]	N/A[e]	< 0.1%
23.34	0.299	0.007	unidentified
23.55	0.78	0.02	unidentified
23.98	5.5	0.2	unidentified
24.06	0.73	0.02	unidentified
24.20	0.102	0.004	unidentified
24.27	0.296	0.008	unidentified
24.48	0.45	0.01	unidentified
24.54	0.57	0.02	unidentified
24.60	0.080	0.002	< 0.1%
24.68	0.108	0.002	unidentified
24.75	0.73	0.02	unidentified
24.82	0.197	0.004	unidentified
24.92	0.111	0.002	unidentified
24.98	0.125	0.003	unidentified
25.09	0.083	0.001	< 0.1%
25.15	0.095	0.002	unidentified
25.23	0.279	0.005	unidentified
25.36	1.09	0.02	unidentified
25.43	0.90	0.02	unidentified
25.47	0.261	0.005	unidentified
25.50	0.132	0.002	unidentified

Characterization of DCPD/Codimer Concentrate

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Table II (continued)

Average Retention Time[a] (min)	Average Area %[a, h]	Standard Deviation[a, h]	Component Identification[b]
25.55	0.097	0.001	unidentified
25.62	0.66	0.01	unidentified
25.76	2.67	0.04	THI[f]
25.84	0.219	0.003	unidentified
25.90	0.179	0.002	unidentified
25.96	0.227	0.003	unidentified
26.00	0.222	0.002	unidentified
26.07	0.116	0.001	unidentified
26.12	0.222	0.001	unidentified
26.16	0.272	0.003	unidentified
26.19	0.618	0.004	unidentified
26.27	2.52	0.02	unidentified
26.33	0.698	0.004	unidentified
26.38	0.665	0.004	unidentified
26.48	0.522	0.003	unidentified
26.54	0.107	0.003	unidentified
26.63	2.20	0.01	DCPD[g] isomer 1
26.73	0.196	0.005	unidentified
26.84	28.6	0.1	DCPD[g] isomer 2
26.94	0.5	0.1	unidentified
26.97[c]	0.236[c]	0.004[c]	unidentified
27.02	0.129	0.004	unidentified
27.14	1.21	0.02	unidentified
27.18	7.49	0.04	unidentified
27.25	1.115	0.003	unidentified
27.30	0.702	0.005	unidentified
27.37	0.194	0.002	unidentified
27.41	0.948	0.007	unidentified
27.51	0.150	0.003	unidentified
27.58	0.280	0.004	unidentified

Characterization of DCPD/Codimer Concentrate

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Table II (continued)

Average Retention Time[a] (min)	Average Area %[a, b]	Standard Deviation[a, b]	Component Identification[b]
27.67	0.134	0.003	unidentified
27.70	0.067	0.002	< 0.1%
27.87	4.70	0.04	unidentified
27.91	1.28	0.02	unidentified
27.99	3.36	0.04	unidentified
28.13	4.14	0.05	unidentified
28.23	0.338	0.005	unidentified
28.30	0.74	0.01	unidentified
28.34	0.134	0.002	unidentified
28.38	0.534	0.009	unidentified
28.42	0.68	0.01	unidentified
28.48	0.158	0.003	unidentified
28.54	0.092	0.002	< 0.1%
28.60	0.207	0.004	unidentified
28.64	1.25	0.02	unidentified
28.73	4.10	0.07	unidentified
28.87	0.56	0.01	unidentified
28.93	0.076	0.002	< 0.1%
28.96	0.079	0.002	< 0.1%
29.06	0.385	0.007	unidentified
29.17	3.76	0.08	unidentified
29.21	0.129	0.004	unidentified
29.29	0.226	0.005	unidentified
29.32	0.119	0.002	unidentified
29.35	0.322	0.007	unidentified
29.48	0.106	0.002	unidentified
29.56	0.162	0.004	unidentified
29.71	0.139	0.004	unidentified
29.75[c]	0.062[c]	0.001[c]	< 0.1%
29.81	0.118	0.003	unidentified
29.89	0.069	0.002	< 0.1%

Characterization of DCPD/Codimer Concentrate

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Table II (continued)

Average Retention Time[a] (min)	Average Area %[a, h]	Standard Deviation[a, h]	Component Identification[b]
29.93	0.108	0.003	unidentified
30.00	0.124	0.002	unidentified
30.06	0.076	0.002	< 0.1%
30.11	0.360	0.009	unidentified
30.14	0.301	0.007	unidentified
30.21	0.166	0.003	unidentified
30.30	0.341	0.009	unidentified
30.36[c]	0.065[c]	0.001[c]	< 0.1%
30.41	0.317	0.008	unidentified
30.51[c]	0.0652[c]	0.0004[c]	< 0.1%
30.57	0.179	0.003	unidentified
30.59	0.161	0.006	unidentified
30.72	0.075	0.002	< 0.1%
30.85	0.159	0.004	unidentified
30.89	0.109	0.002	unidentified
31.08	0.119	0.003	unidentified
31.31	0.113	0.002	unidentified
31.62	0.123	0.004	unidentified
31.69	0.080	0.002	< 0.1%
32.29	0.126	0.006	unidentified
32.59	0.171	0.006	unidentified
32.81	0.077	0.003	< 0.1%
32.84	0.080	0.004	< 0.1%
33.16	0.111	0.006	unidentified
33.23	0.067	0.003	< 0.1%
33.37	0.076	0.004	< 0.1%
33.73[d]	0.065[d]	N/A[e]	< 0.1%
34.42[d]	0.059[d]	N/A	< 0.1%
35.12	0.087	0.006	< 0.1%

[a] Based on three replicate analyses
[b] Components present at > 0.1% but without commercially available standards were not identified, components present at < 0.1% were indicated as such.
[c] Based on two results. Component not detected in one of the three replicates.
[d] Based on a single result. Component not detected in two of the three replicates.
[e] N/A stands for Not Applicable.
[f] THI stands for 3a, 4, 7, 7a-tetrahydroindene.
[g] DCPD stands for dicyclopentadiene.
[h] Area % and Standard Deviation rounded to reflect experimental precision of the particular measurement.

Characterization of DCPD/Codimer Concentrate

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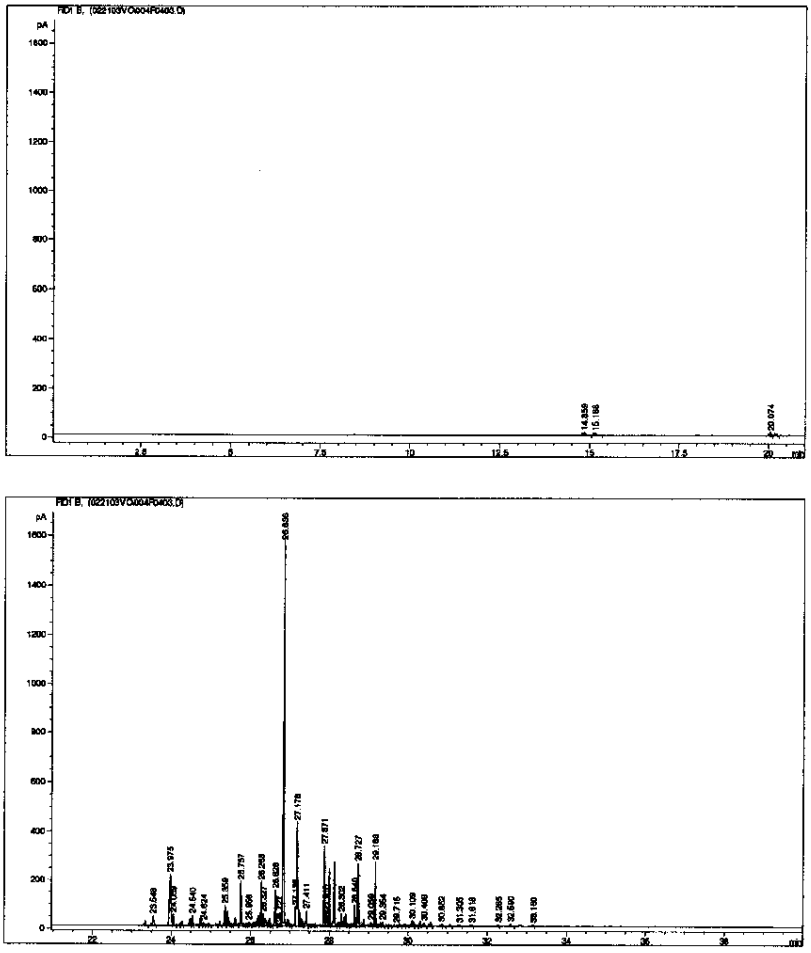
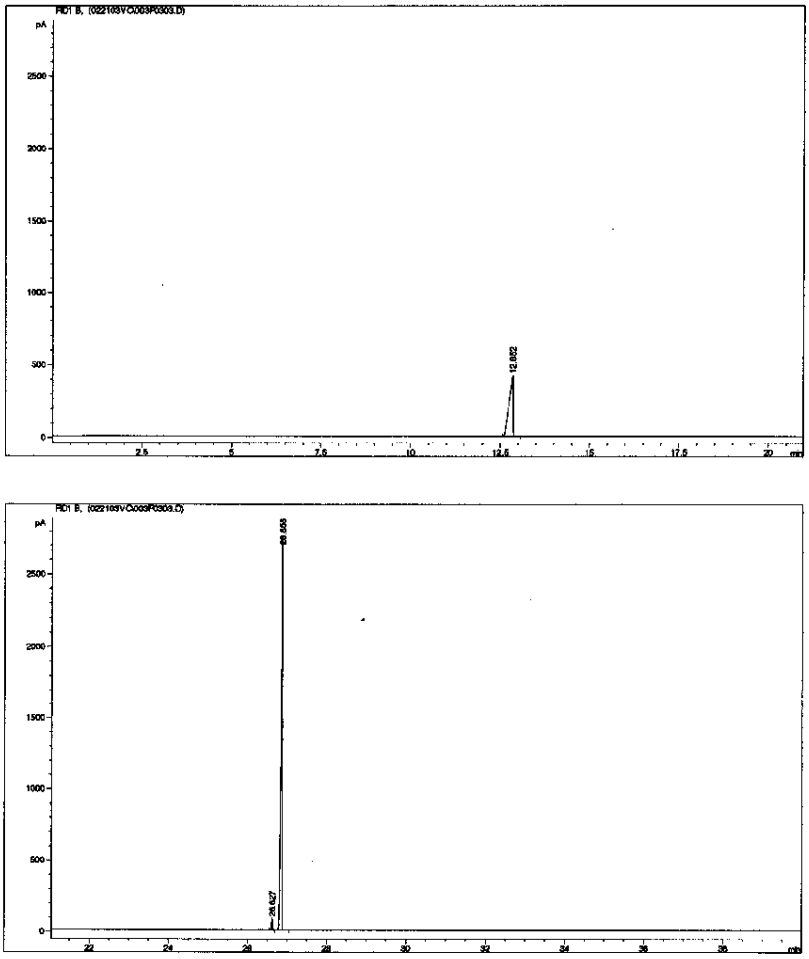
Figure 1
Representative chromatogram of DCPD/Codimer Concentrate test substance. Chromatogram is split to two sections due to complexity of the test substance composition.



Characterization of DCPD/Codimer Concentrate

DuPont – 11642

Figure 2
Representative chromatogram of dicyclopentadiene (DCPD) reference substance (137 mg/g in chloroform). DCPD elutes as two isomers at approximately 26.63 and 26.86 minutes. Chloroform elutes at approximately 12.9 minutes. Chromatogram is split to two sections for consistency with the test substance chromatogram.



- 15 -

Characterization of DCPD/Codimer Concentrate

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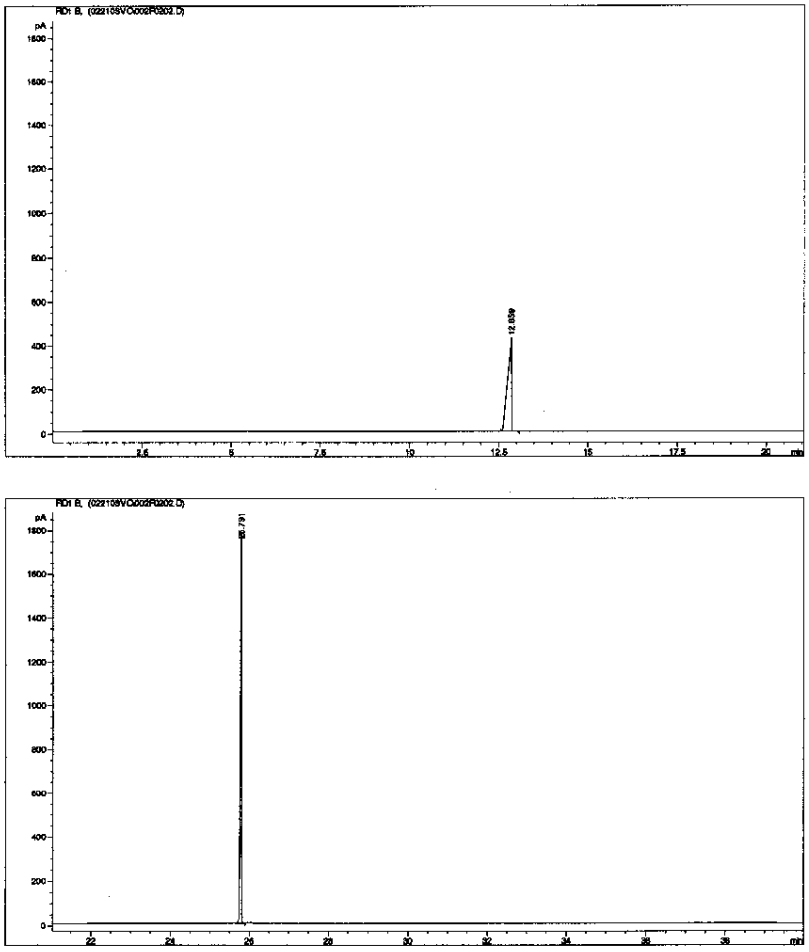
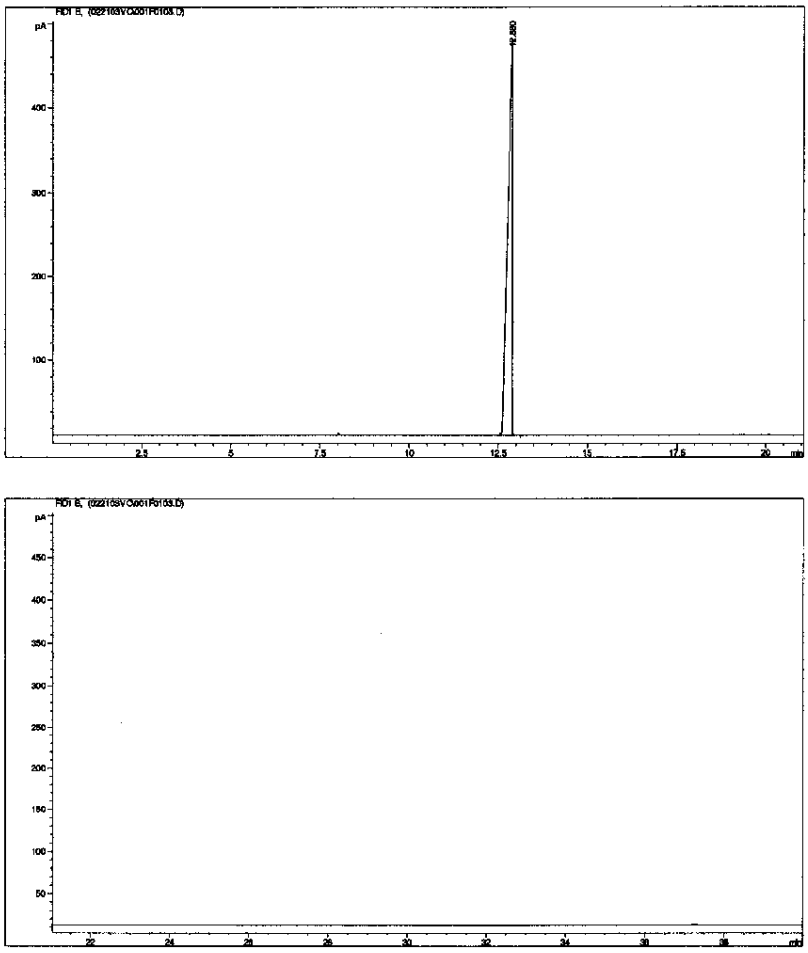
Figure 3
Representative chromatogram of 3a, 4. 7, 7a-tetrahydroindene (THI) reference substance (78 mg/g in chloroform). THI elutes at approximately 25.79 minutes. Chloroform elutes at approximately 12.9 minutes. Chromatogram is split to two sections for consistency with the test substance chromatogram.



Characterization of DCPD/Codimer Concentrate

DuPont – 11642

Figure 4
Representative chromatogram of the chloroform solvent. Chloroform elutes at approximately 12.9 minutes. Chromatogram is split to two sections for consistency with the test substance chromatogram.



APPENDIX 1

Study Protocol

Characterization of Dicyclopentadiene/Codimer Concentrate (23 pages).

DuPont – 11642

PROTOCOL

1. TITLE
Characterization of Dicyclopentadiene/Codimer Concentrate (DCPD/Codimer Concentrate).

2. PURPOSE
The purpose of this study is to characterize the DCPD/Codimer Concentrate for use as a Test Substance in GLP studies.

3. STUDY SPONSOR
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

Sponsor Representative: Elizabeth J. Moran, Ph.D., Manager, American Chemistry Council

4. TESTING FACILITY
DuPont Haskell Laboratory for Health and Environmental Sciences
1090 Elkton Rd.
Newark, DE 19714

Study Director: Vladimir Capka, Ph.D., Research Chemist

5. STUDY NUMBER
DuPont Study Number: DuPont-11642
Work Request Number: 14294
Study Code Number: 378
American Chemistry Council Reference Number: OLF-92.0-HPV789-DHL

6. PROPOSED EXPERIMENTAL TIME-FRAME
Experimental Start Date: 17 January 2003
Experimental Termination Date: 4 April 2003

The actual start and termination dates will be documented in the study records and final report.

7. TEST AND REFERENCE SUBSTANCES

A. TEST SUBSTANCE

Identification: Dicyclopentadiene/ Codimer Concentrate – Supplied by Sponsor for batch being used in study.
Upon receipt at the testing facility, the Test Substance was uniquely identified by Haskell Laboratory Test Substance number 25430.
Synonyms: DCPD/Codimer Concentrate
DCP 97

Chemical Formula: Not applicable. A complex hydrocarbon mixture of variable concentration. Carbon range is C9 to C12.
CAS Number: 68478-10-4

B. REFERENCE SUBSTANCES

Reference substances used in the study will be obtained from commercial sources and will be used for component identification for components with concentrations higher than 0.1 % as indicated by the actual test substance lot analysis supplied by the sponsor. The following commercially available reference substances will be used for component identification of the DCPD/Codimer Concentrate test substance based on retention time:

- dicyclopentadiene (DCPD, mixture of endo- and exo-)*, CAS Number: 77-73-6
- 3a, 4, 7, 7a-tetrahydroindene, CAS Number: 3048-65-5

Reference substances that were used in the study will be identified in the study records and final report.

* DCPD will be quantified (based on area %) as sum of endo- and exo- isomers.

8. METHODS

The method used for characterization of DCPD/Codimer Concentrate will be based on the method provided by the sponsor. The method provided by the sponsor is in Appendix 1. The actual method for test substance characterization will measure area percent purity within a given sample. Gas chromatographic (GC) analysis will be performed using triplicate injections of representative portions of a sample.
The instrument and the experimental conditions pertaining to the GC analysis are summarized below:

Instrument:	Hewlett Packard HP6890 gas chromatograph with 7683 autosampler
GC Column:	DB-1, J&W, 50 m length, 0.25 mm internal diameter, 0.25 µm film thickness
Carrier Gas:	Helium
Injector Temperature:	180°C
Pressure:	17.6 psi
Split Ratio:	100:1
Wash Solvent A:	hexane
Wash Solvent B:	chloroform
Syringe Size:	5 µL
Injection Volume:	0.1 µL
Carrier Gas Flow Rate:	1.4 mL/min, constant flow mode
Initial Temperature:	-10°C, increase at 2°C/min to Final Temperature 1
Final Temperature 1:	20°C, increase at 10°C/min to Final Temperature 2
Final Temperature 2:	250°C, hold at Final Temperature 2 for 2 minutes
Run Time:	40 min
Detector:	Flame Ionization Detector (FID)

Detector Temperature:	280°C
Hydrogen Flow:	40 mL/min
Air Flow:	450 mL/min
Makeup Gas Type:	Helium

The actual experimental parameters might be modified if necessary. All such modifications (if any) will be documented in the study records with appropriate reasons for the adjustments. Peak areas from chromatograms will be obtained for all sample-related peaks that result in area greater than 0.1 % of the total peak area. Area percent is calculated using the following calculation

$$area\%_i = \frac{area_i}{\sum_{i=1}^{n} area_i} \times 100\%$$

n is the number of integrated chromatographic peaks in the test substance chromatogram, $area_i$ and $area\%_i$ are the chromatographic peak area and the area % of the i-th component, respectively.
Identity of test substance components will be confirmed by comparing the GC retention time of components with those of reference standards as indicated in section 7B.

9. STATISTICAL METHODS
Not applicable. Only basic averaging will be used.

10. RECORDS TO BE MAINTAINED
At the completion of the study, all original study raw data, protocol, and a copy of the final report will be archived by the performing laboratory for ten years. After the ten-year archiving period, all study-specific raw data, including the original protocol will be transferred to the sponsor unless instructed otherwise. The performing laboratory will also maintain site-specific/facility raw data.

11. REPORTING
The reporting will be the responsibility of the study director and will be in form of a final report. The final report will contain description of analytical method that was used, statement of material composition composition, and identification for components that were commercially available as standards. Components without commercially available analytical standards will be listed based on their retention times.

12. GOOD LABORATORY PRACTICE COMPLIANCE
This study will be conducted in accordance with U.S. EPA Good Laboratory Practice Standards (GLPs) of TSCA 40 CFR Part 792, which are consistent with OECD Principle of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98)17. A statement of compliance will be included in the final report. Signatures of the study director, collaborating scientists, and supervisory personnel will attest to the authenticity of the study.

13. QUALITY ASSURANCE

Conduct and protocol reviews will be performed by the testing facility quality assurance unit. The study raw data and the report will be audited by the testing facility quality assurance unit prior to being sent to the sponsor.

14. PROTOCOL APPROVAL

Vladimir Capka

29-Jan-2003

Vladimir Capka, Ph.D., Research Chemist
Study Director
DuPont Haskell Laboratory for Health and Environmental Sciences

Date

Elizabeth J. Morgan

Feb 3, 2003

Elizabeth J. Morgan, Ph.D., Manager
Sponsor Representative
American Chemistry Council

Date

DuPont – 11642

APPENDIX 1

Analytical method for DCPD/Codimer Concentrate analysis provided by the sponsor.

INSERTED AS RECEIVED V.C. 14 Mar-2002

BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE	BASIC CHEMICALS
BRCP 4506 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	PAGE 1 OF 22 DATE: 10/28/98

1.0 SCOPE

This method provides capillary GC analyses for DCPD, MCPD, ECR 602, XR–01 Cracker Feed and UT–71 Overhead. It also provides formulas and a computer program for estimating the amount of CPD and MCPD monomers available upon thermal cracking (retro–Diels Alder reactions). This program is called CAM, for calculated available monomer, and replaces the old "cracker GC" for prime products. A second program called CAM2 provides formulas for estimating the amount of CPD and MCPD monomers available from cyclodiene concentrate.

2.0 REFERENCE

2.1. MSDS for all chemicals involved

2.2. Work Instruction BC 303

2.3. Before changing this procedure, it must be checked for product representation compliance

3.0 SAFETY

3.1. The samples to be analyzed are volatile, flammable organics and should be treated as such. Nitrile gloves should provide adequate personal protection. Since some of these samples contain low levels of benzene, breathing the vapors and skin contact should be avoided and the samples should be kept capped as much as possible. Consult MSDS for further toxicity data.

4.0 APPARATUS

4.1. Hewlett/Packard 5890 gas chromatograph or equivalent with flame ionization detector and split injector.

4.2. Automatic injection apparatus capable of delivering 0.1 µL sample

4.3. 5.0 µL auto injector syringe

4.4. 2 mL screw cap septum vials

4.5. Disposable plastic jumbo pipettes

4.6. 50 M x 0.25 mm DB–1 capillary column, 0.25 micron film thickness.

4.7. HP–3392A plotter integrator, or the equivalent

5.0 REAGENTS

5.1. Reagent grade hexane for syringe rinse.

BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 2 OF 22 DATE: 10/28/98

6.0 INSTRUMENT SETUP

Typical GC Parameters

Injection Port (A side)	180°C
Detector	280°C
Initial Temperature	–10°C
Initial Time	0 min
Ramp Rate	2°C/min
Final Temperature	20°C
Final Time	0 min
Rate A	10°C/min
Final Temperature A	250°C
Final Time A	23 min
Sample Size	.1 µL
Carrier Gas (Helium)	24.5 psi, 1 cc/min
Make–up Gas (Helium)	70 psi, 30 cc/min
Detector Air	19 psi
Split Flow @ 75°C	75 cc/min
Septum Purge Flow @ 75°C	3–5 cc/min

7.0 CALIBRATION

Not applicable. All response factors equal 1.0.

8.0 PROTOCOL

ACTION	NOTES
8.1. Load the solvent bottle with hexane.	
8.2. Fill an autoinjector vial with sample and load onto the autoinjector.	Check sample for presence of solids prior to analysis. Filter the sample if necessary.
8.3. Choose the appropriate workfile and CALS method.	
8.4. Start the analysis by depressing the "start" button on the integrator.	

9.0 CALCULATIONS

9.1. If CAM results for prime products are required, they can be calculated by the CALS computer system. A representative CALS printout which is produced when the CAM program is run, is shown in Appendix 12.3.4. Alternately, the QuickBasic program listed in Appendix 12.3.1 can be employed at any PC. Lastly, the calculation can be carried out by hand, if necessary, using the equations listed in Appendix 12.3.1.

9.2. Calculated Available Monomer (CAM): After the CALS report has been printed, ensure that no peaks are un-identified. If unknowns exist, CAM program will not give a total of 100.00 and results will be incorrect. Method must be modified to call all peaks correctly before running CAM program.

xxRTE-A CALS: BA,CAM::112 — Runs HP1000 BASIC which schedules program CAM.

> RUN — Type in RUN at the BASIC prompt (>) to begin executing CAM.

Calculated Available Monomer Program Menu

CAM PROGRAM [1]

CAM2 PROGRAM [2]

EXIT TO The Basic Prompt [3]

Enter Menu Selection 1 — Refer to Post Manual for correct program (CAM or CAM2)

Calculated Available Monomer Program

Enter CALS Filename: CA334 — Prompts you to enter the CALS file name.

Hardcopy Printout Desired? [Y],N: — Default is Y for Yes. If you press the Return key the output will go to LU86. If you type N and press RETURN the output will go to the CAM PROGRAM MENU.

ENTER MENU SELECTION 3 — Exits to Basic Prompt

> BYE — Exits to CALS

Record the data on the cracked CG log sheet, noting it as CAM results.

9.3. If CAM2 results for CDC, XR-01 Feed or UT-71 Btms are required, they can be calculated by employing the CAM2 program as in 9.1. A copy of the QuickBasic program is listed in Appendix 12.3.2.

10.0 REPORTING

Enter data into LINS to two decimal places.

11.0 QUALITY CONTROL

The quality control samples are DCPD and MCPD unit samples.

BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 4 OF 22 DATE: 10/28/98

12.0 APPENDIX

12.1. TYPICAL CHROMATOGRAMS DCPD

12.1.1.

Normalization Area Analysis

File: Q2000 DCP 20:34:26 5/05/1992

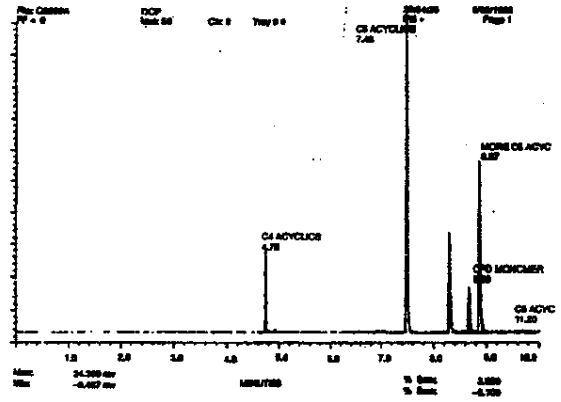
Mthd: 3062 Inst Chnl 6 Vial # 0 Std/Smpl % 100.000

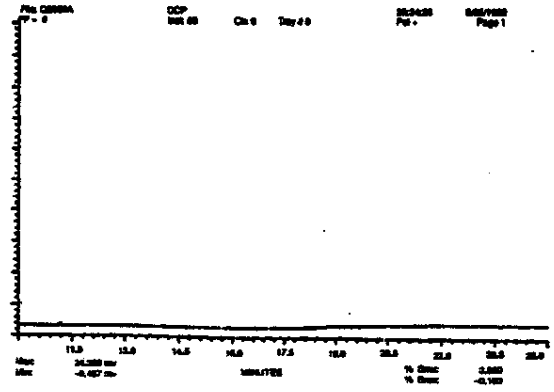
Mthd: 3062 QC 10:24:46 5/07/1992

Name	WT%	Pk	RRT	RRF	Area	Height
C4 ACYCLICS	0.1267	002	4.76	1.0000	7.844	5.661
C5 ACYCLICS	1.0301	006	7.48	1.0000	63.776	23.504
CPD MONOMER	0.1086	001	8.69	1.0000	6.726	3.247
MORE C5 ACYC	0.5016	001	8.87	1.0000	31.057	12.894
C6 ACYCLICS	0.0244	003	11.20	1.0000	1.513	0.241
BENZENE			17.00	1.0000		
TOLUENE			21.96	1.0000		
MCPD MONOMER			16.00	1.0000		
MORE C6 ACYC			17.65	1.0000		
C7 CYCLICS			20.60	1.0000		
C8 ALI+ARO			24.90	1.0000		
C4–CPD CODIM	0.1168	001	25.85	1.0000	7.233	3.082
C4–MCPD CODI	0.0363	002	26.22	1.0000	2.250	0.635
C5 ACY.DIM	0.0099	002	27.52	1.0000	0.616	0.180
TETRAHINDENE	0.0161	BCV	28.00	1.0000	0.994	0.453
C5–CPD CODIM	0.3433	006	28.61	1.0000	21.253	6.576
exo–DCPD	0.6267	001	29.06	1.0000	38.797	11.624
endo–DCPD	95.7042	001	29.46	1.0000	5925.223	796.992
C5–MCPD CODI	0.1295	003	29.76	1.0000	8.017	1.625
CPD–MCPD COD	0.4946	003	30.82	1.0000	30.625	4.877
MCPD DIMERS			33.00	1.0000		
CDPD–C7 DIM			35.75	1.0000		
TRIMERS	0.7310	006	38.40	1.0000	45.256	13.143
	100.0000				6191.180	

BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 5 OF 22 DATE: 10/28/96

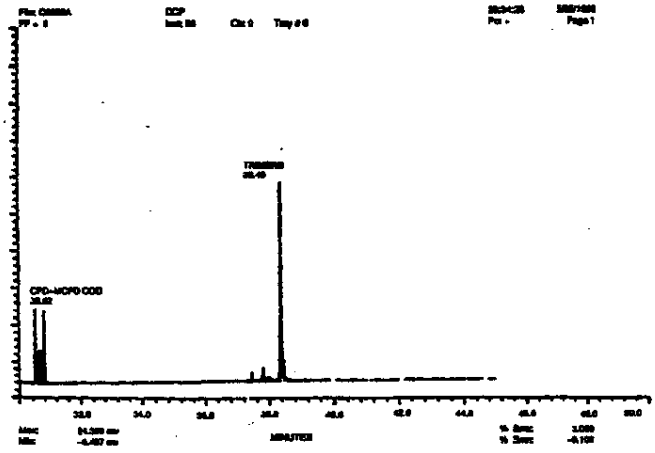
12.1.2.





BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 6 OF 22 DATE: 10/28/98

12.1.3.



BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMCIALS PAGE 7 OF 22 DATE: 10/28/96

12.1.4. MCPD DIMER CONC

Normalization Area Analysis

File: HW606 8:20:52 5/06/1992

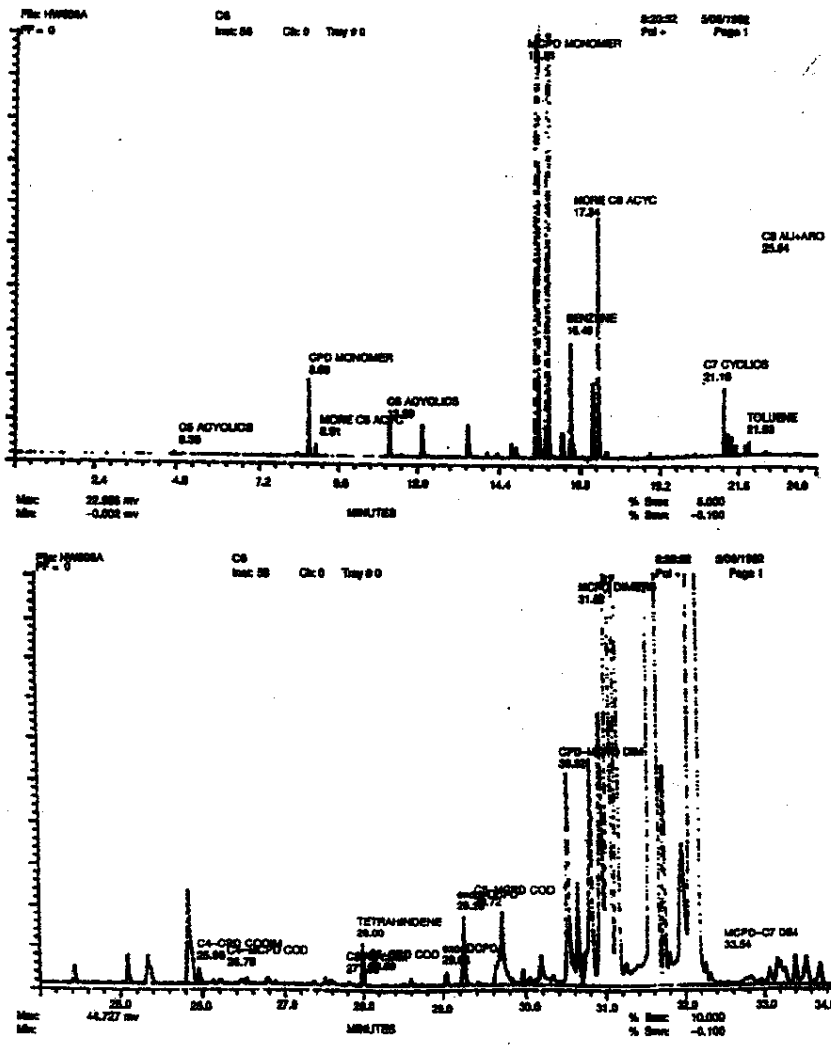
Mthd: 3063 Inst Chnl 6 Vial # 0 Std/Smpl % 100.000

Mthd: 3063 MCPD 10:15:06 5/07/1992

Name	WT%	Pk	RRT	RRF	Area	Height
C4 ACYCLICS			0.80	1.0000		
C5 ACYCLICS	0.0113	003	8.35	1.0000	0.592	0.146
CPD MONOMER	0.1429	VCV	8.68	1.0000	7.514	3.787
MORE C5 ACYC	0.0249	001	8.914	1.0000	1.300	0.607
C6 ACYCLICS	0.4501	012	13.50	1.0000	23.668	1.668
MCPD MONOMER	10.6639	004	15.51	1.0000	560.806	94.365
BENZENE	0.3139	VCV	16.49	1.0000	16.510	5.833
MORE C6 ACYC	0.8806	015	17.34	1.0000	46.321	12.025
C7 CYCLICS	0.3040	006	21.16	1.0000	15.987	3.380
INDENE	0.0283	VCB	213.93	1.0000	1.490	0.635
C8 ALI+ARO	0.9158	011	25.84	1.0000	48.163	9.899
C4–CPD CODIM	0.0893	003	25.96	1.0000	4.696	1.395
C4–MCPD CODI	0.1826	012	26.79	1.0000	9.600	0.840
C5 ACY.DIM	0.0189	001	27.82	1.0000	0.993	0.326
TETRAHINDENE	0.1609	VCV	28.00	1.0000	8.463	4.116
C5–CPD CODIM	0.0992	010	28.60	1.0000	5.216	0.698
exo–DCPD	0.0513	002	29.04	1.0000	2.695	1.173
endo–DCPD	0.2961	001	29.26	1.0000	15.572	7.090
C5–MCPD COD	1.0739	010	29.72	1.0000	56.474	7.657
CPD–MCPD DIM	1.6473	002	30.52	1.0000	86.629	22.190
MCPD DIMERS	81.2394	014	31.62	1.0000	4272.306	438.781
MCPD–C7 DIM	1.2007	012	33.54	1.0000	63.145	2.906
TRIMERS	0.2046	016	40.51	1.0000	10.762	0.724
	100.0000				5258.910	

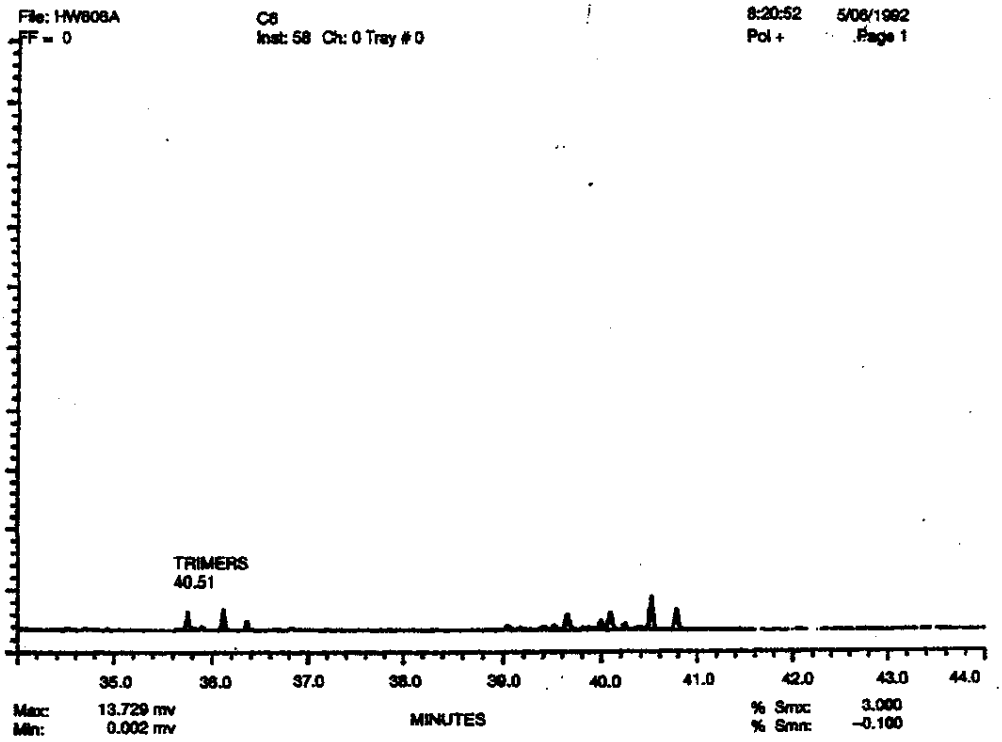
BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 8 OF 22 DATE: 10/28/96

12.1.5.



BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 9 OF 22 DATE: 10/28/98

12.1.6.



BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE	BASIC CHEMICALS
BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	PAGE 10 OF 22 DATE: 10/28/98

12.1.7. DCPD/COLIMER CONC.

Normalization Area Analysis

File: HW613 13:46:57 5/06/1992

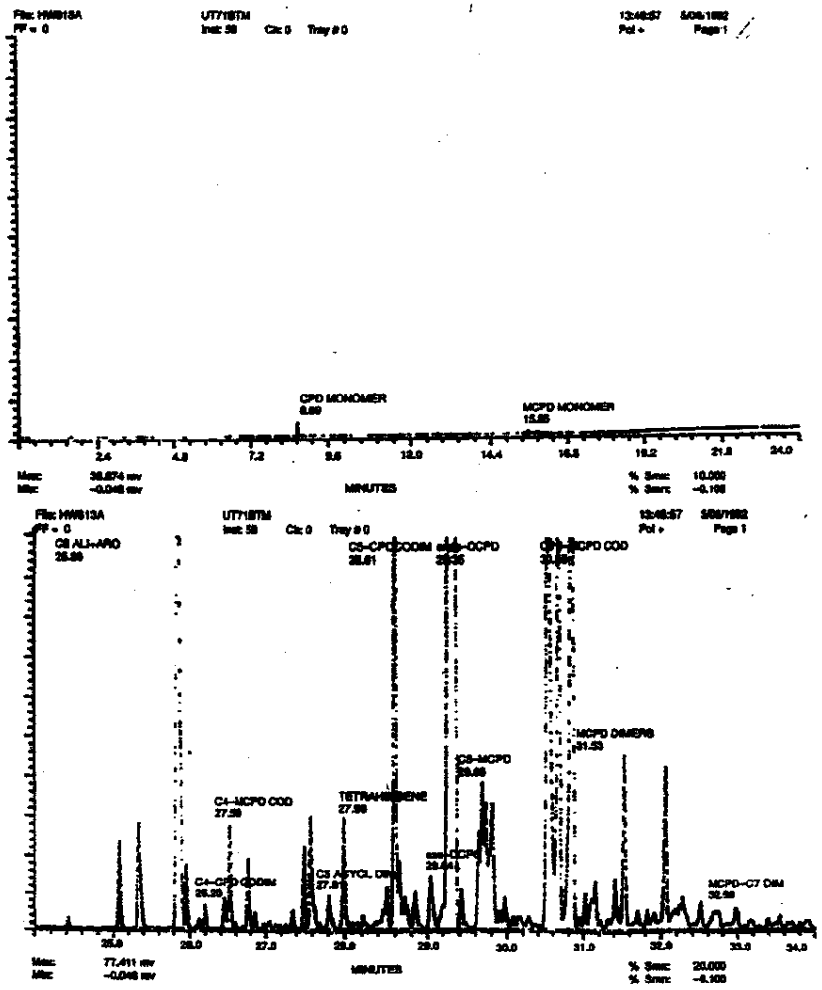
Mthd: 3064 Inst Chnl 6 Vial # 0 Std/Smpl % 100.000

Mthd: 3064 CDC 10:46:37 5/07/1992

Name	WT%	Pk	RRT	RRF	Area	Height
CPD MONOMER	0.0542	BCB	8.69	1.0000	2.728	1.245
C4 ACYCLICS			2.35	1.0000		
C5 ACYCLICS			6.60	1.0000		
MORE C5 ACYC			9.15	1.0000		
C6 ACYCLICS			12.45	1.0000		
MCPD MONOMER	0.0248	002	15.55	1.0000	1.248	0.243
BENZENE			16.65	1.0000		
TOLUENE			21.92	1.0000		
MORE C6 ACYC			18.89	1.0000		
C7 CYCLICS			21.49	1.0000		
C8 ALI+ARO	9.7586	013	25.86	1.0000	491.114	125.551
C4–CPD CODIM	0.3095	002	26.20	1.0000	15.578	4.869
C4–MCPD CODI	4.2285	015	27.59	1.0000	212.806	22.504
C5 ACY DIM	0.4820	003	27.81	1.0000	24.259	6.954
TETRAHINDENE	1.0142	VCV	27.99	1.0000	51.043	22.317
C5–CPD CODIM	6.6673	012	28.61	1.0000	335.543	86.372
exo–DCPD	0.7718	001	29.04	1.0000	38.842	11.041
endo–DCPD	33.8022	002	29.35	1.0000	1701.144	382.626
C5–MCPD	6.9038	015	29.69	1.0000	347.445	29.190
CPD–MCPD COD	21.8391	003	30.55	1.0000	1099.083	143.130
MCPD DIMERS	8.0402	020	31.53	1.0000	404.633	34.305
MCPD–C7 DIM	2.6178	028	32.98	1.0000	131.744	4.361
TRIMERS	3.4858	063	35.64	1.0000	175.426	6.221
	100.0000				5032.836	

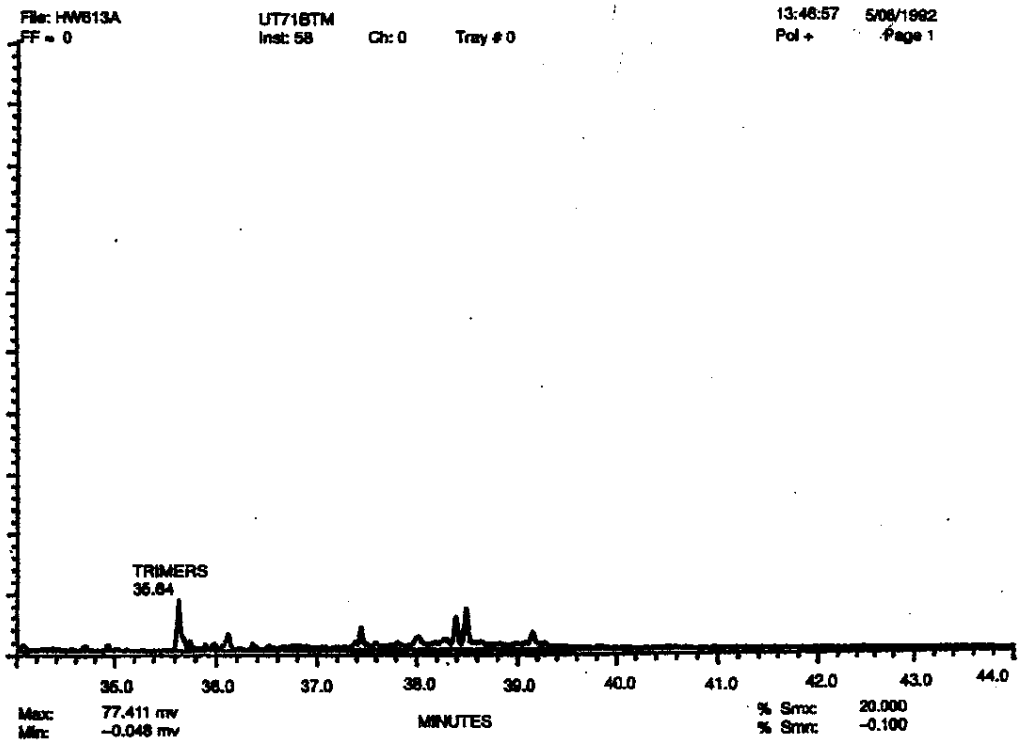
BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 11 OF 22 DATE: 10/28/98

12.1.8.



BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 12 OF 22 DATE: 10/28/98

12.1.9.



BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 13 OF 22 DATE: 10/28/98

12.1.10. DCPD /codimer conc

Normalization Area Analysis

File: L0883 10:55:42 4/21/1992

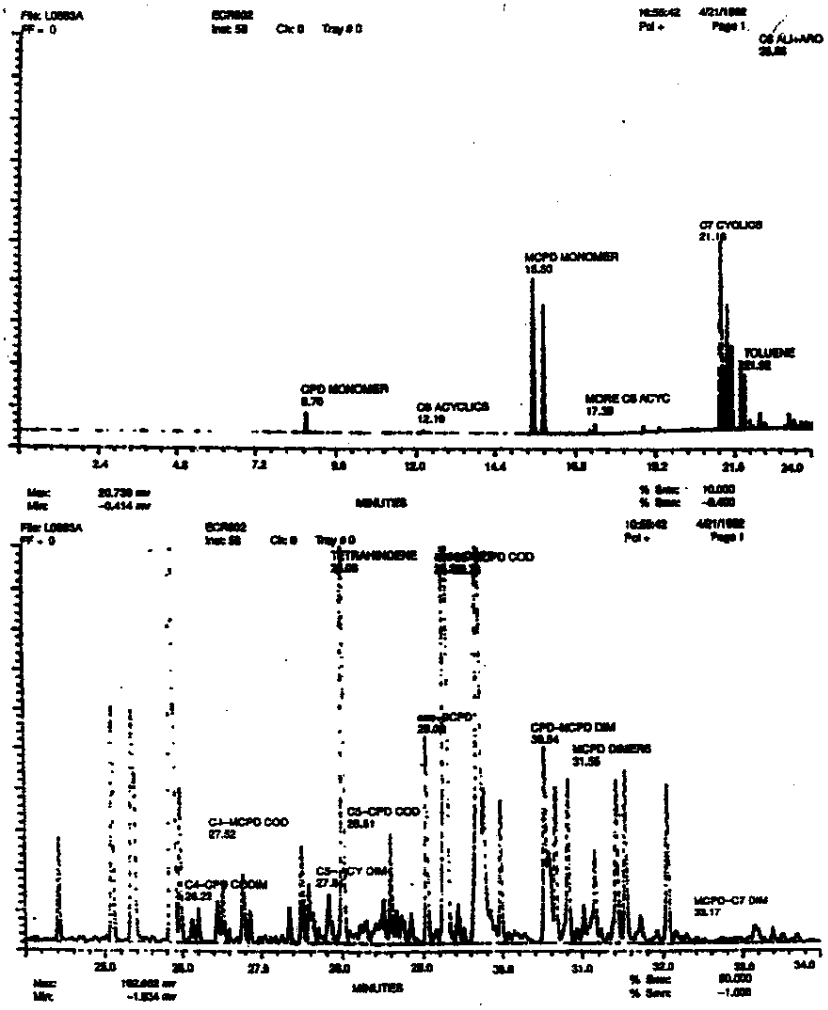
Mthd: 3061 Inst Chnl 6 Vial # 0 Std/Smpl % 100.000

Mthd: 3061 ECR602 13:39:58 5/07/1992

Name	WT%	Pk	RRT	RRF	Area	Height
CPD MONOMER	0.0411	BCB	8.70	1.0000	1.949	0.964
C4 ACYCLICS			0.80	1.0000		
C5 ACYCLICS			4.19	1.0000		
MORE C5 ACYC			10.04	1.0000		
C6 ACYCLICS	0.0071	001	12.19	1.0000	0.336	0.132
MCPD MONOMER	0.8722	002	15.50	1.0000	41.356	7.677
BENZENE			16.34	1.0000		
MORE C6 ACYC	0.0892	006	17.39	1.0000	4.230	0.484
C7 CYCLICS	1.4726	007	21.16	1.0000	69.822	9.257
TOLUENE	0.1274	VCV	21.92	1.0000	6.040	2.616
C8 ALI+ARO	22.3858	039	25.88	1.0000	1061.429	184.843
C4–CPD CODIM	0.7793	003	26.22	1.0000	36.959	8.850
C4–MCPD COD	5.7796	015	27.52	1.0000	274.044	24.839
C5 ACY DIM	1.1098	004	27.84	1.0000	52.620	12.580
TETRAHINDENE	5.9611	VCV	28.03	1.0000	282.646	112.212
C5–CPD COD	4.9996	013	28.61	1.0000	237.057	27.875
exo–DCPD	2.6816	002	29.06	1.0000	127.148	51.722
endo–DCPD	13.1151	001	29.31	1.0000	621.854	200.054
C5–MCPD COD	16.3405	012	29.73	1.0000	774.790	142.227
CPD–MCPD DIM	8.7192	005	30.54	1.0000	413.425	49.318
MCPD DIMERS	10.9581	015	31.55	1.0000	519.580	43.556
MCPD–C7 DIM	2.7982	028	33.17	1.0000	132.679	4.752
TRIMERS	1.7626	039	36.41	1.0000	83.576	2.458
	100.0000				4741.533	

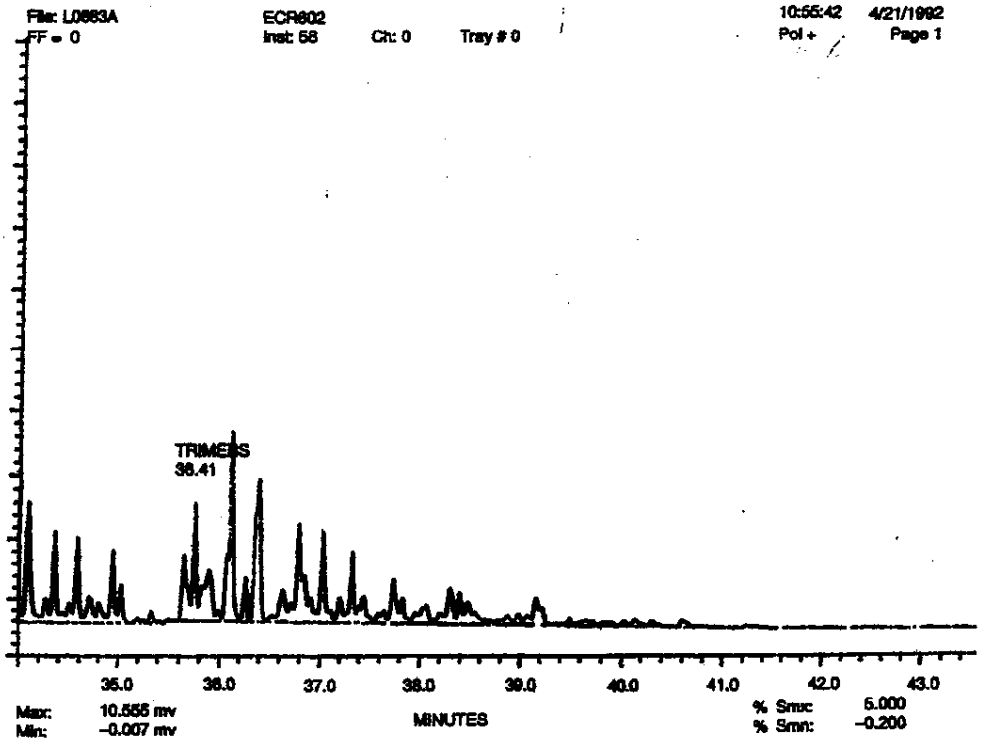
BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 14 OF 22 DATE: 10/28/96

12.1.11.



BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 15 OF 22 DATE: 10/28/96

12.1.12.



BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 16 OF 22 DATE: 10/28/96

TOLUENE STREAM

12.1.13.

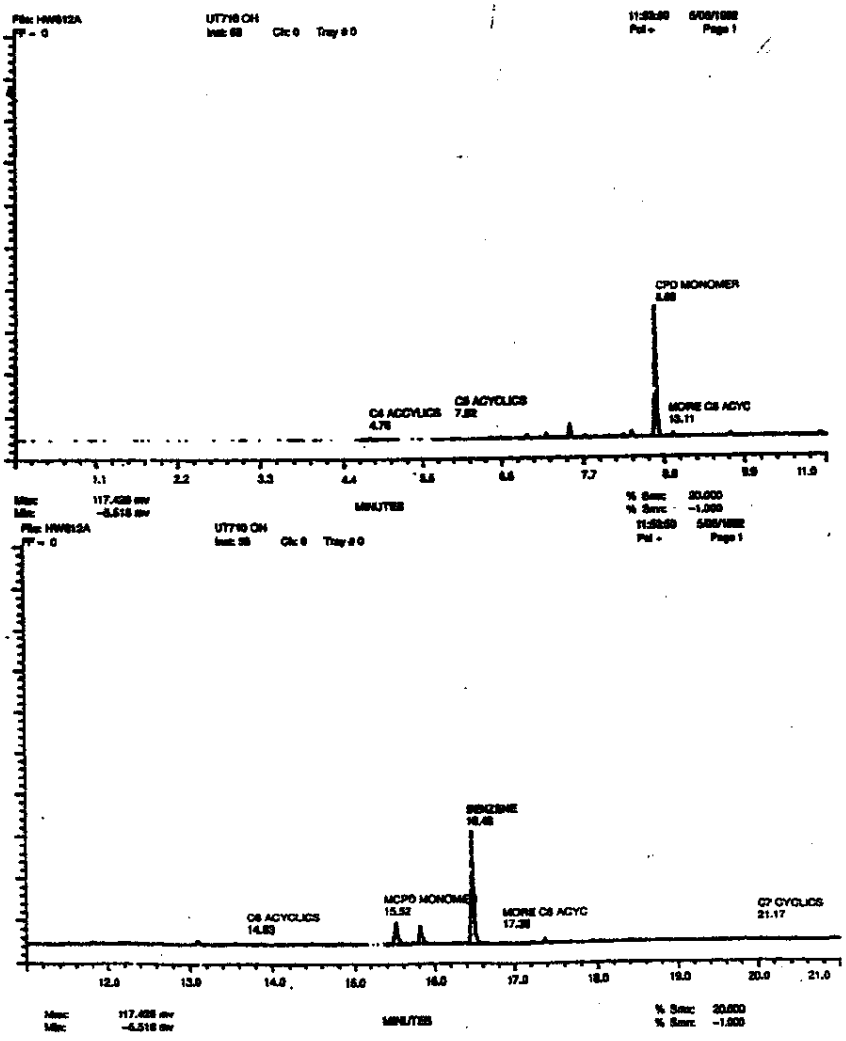
Normalization Area Analysis

File: HW612 UT710 OH 11:53:50 5/06/1992
Mthd: 3060 Inst Chnl 6 Vial # 0 Std/Smpl % 100.000
Mthd: 3060 UT710 OH 11:21:48 5/07/1992

Name	WT%	Pk	RRT	RRF	Area	Height
C4 ACYCLICS	0.0070	002	4.76	1.0000	0.420	0.270
C5 ACYCLICS	0.3220	012	7.52	1.0000	19.349	3.748
CPD MONOMER	1.2359	BCB	8.68	1.0000	73.890	36.198
MORE C5 ACYC	0.2105	016	13.11	1.0000	12.585	1.047
C6 ACYCLICS	0.0319	006	14.83	1.0000	1.904	0.261
MCPD MONOMER	0.5234	005	15.52	1.0000	31.291	5.708
BENZENE	1.3200	BCB	16.48	1.0000	78.917	31.943
MORE C6 ACYC	0.1526	015	17.38	1.0000	9.121	1.161
C7 CYCLICS	0.5603	016	21.17	1.0000	33.50	2.748
TOLUENE	87.5514	001	22.14	1.0000	5234.398	582.481
C8 ALI+ARO	8.0387	048	24.44	1.0000	480.605	38.744
C4–CPD CODIM	0.0387	005	26.53	1.0000	2.312	0.420
C5–CPD CODIM			28.49	1.0000		
exo–DCPD			29.10	1.0000		
endo–DCPD	0.0069	001	29.26	1.0000	0.414	0.207
C5–MCPD CODI	0.0009	001	30.52	1.0000	0.054	0.037
CPD–MCPD COD			31.14	1.0000		
MCPD DIMERS			32.22	1.0000		
MCPD–C7 DIM			34.53	1.0000		
TRIMERS			40.50	1.0000		
	100.0000				5978.660	

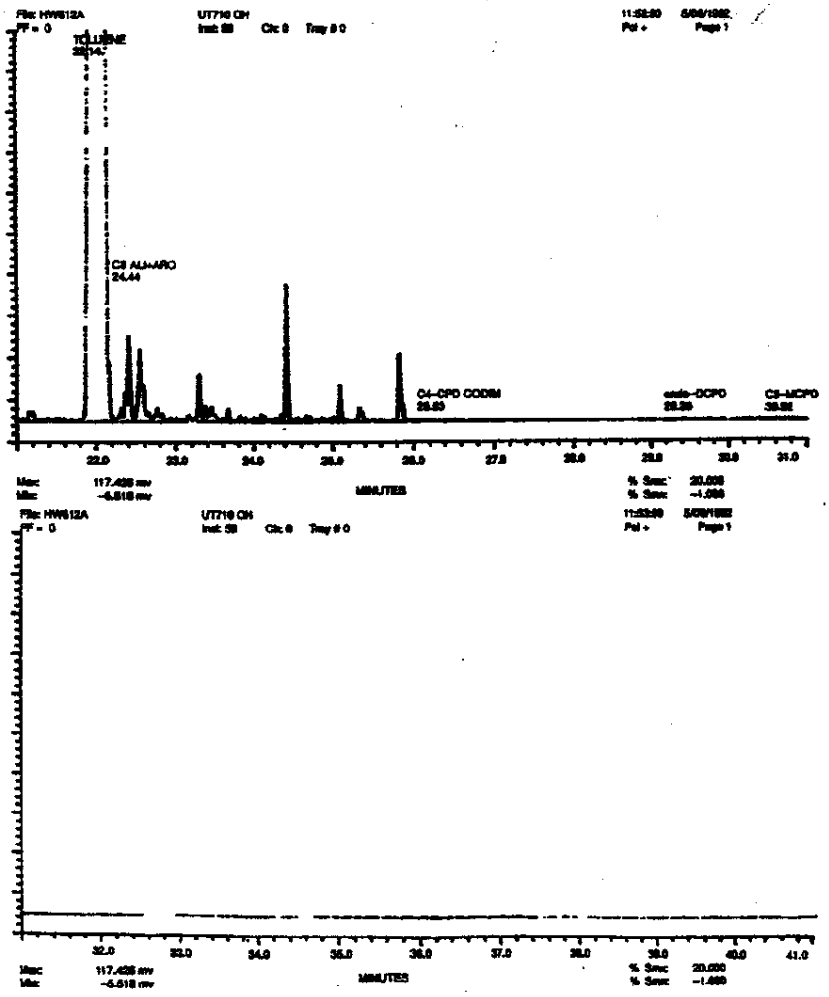
BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 17 OF 22 DATE: 10/28/96

12.1.14.



BATON ROUGE CHEMICAL PLANT LABORATORY PROCEDURE BRCP 4505 Capillary GC and Calculated Available Monomer Analyses of CPLA Streams	BASIC CHEMICALS PAGE 18 OF 22 DATE: 10/29/98

12.1.15.



APPENDIX 2

Study Protocol Amendments.

No study protocol amendments were issued for the current study.

APPENDIX 3

Certificates of Analyses for Dicyclopentadiene and 3a, 4, 7, 7a-Tetrahydroindene Reference Substances.

Product Number: **454338**

Product Name: **Dicyclopentadiene**

Register or Login for Price Info Click Here

Product Information

Description / Pricing
Cert. of Analysis
Enter Lot No
MSDS
Options
Print Preview
Bulk Quote
Ask A Scientist

ALDRICH

Certificate of Analysis

TEST	SPECIFICATION	LOT {14209PI} RESULTS
Product Name	Dicyclopentadiene	
Product Number	454338	
CAS Number	77736	
Formula	$C_{10}H_{12}$	
Formula Weight	132.2	
APPEARANCE	COLORLESS LIQUID OR SOLID	WHITE CRYSTALLINE SOLID
INFRARED SPECTRUM	CONFORMS TO STRUCTURE.	CONFORMS TO STRUCTURE.
GAS LIQUID CHROMATOGRAPHY	CA. 95% (AS A MIXTURE OF ENDO AND EXO)	99.7 % (AS A MIXTURE OF EXO AND ENDO)
QUALITY CONTROL ACCEPTANCE DATE		DECEMBER 2000

David Swessel

David Swessel, Supervisor
Quality Control

11/01/2002 FRI 14:24 FAX 5032831987 TCI America 003/003

H# 22703-248
SAM 11-14-02

TCI AMERICA

CERTIFICATE OF ANALYSIS

T1315
Lot# GK01
CAS# 3048-65-5

3A,4,7,7A-TETRAHYDROINDENE

Appearance:	Colorless Clear Liquid
Assay (GC):	99.0%
SG (20/20):	0.9278
n (20/D):	1.4981

9211N. Harborgate St. Portland, OR 97203 Phone: (503)283-1681 (800)423-8616 Fax: (503)283-1987

Dosing Formulation Analysis

Table I. Recovery of DCPD/Codimer Concentrate Added to Dosing Vehicle

Sample Type	mg/ml DCPD/Codimer Concentrate		Percent
	Nominal	Measured	Nominal
RECOVERY(A)	2.47	2.73	110.5
RECOVERY(B)	2.20	2.15	97.5
RECOVERY(C)	3.20	3.02	94.4
		Mean	***100.8 ± 8.5, C.V. 8%***
RECOVERY(A)	12.9	13.1	101.6
RECOVERY(B)	13.3	13.3	100.0
RECOVERY(C)	13.0	12.0	92.3
		Mean	***98.0 ± 5.0, C.V. 5%***
RECOVERY(A)	52.7	50.4	95.6
RECOVERY(B)	49.3	51.3	104.1
RECOVERY(C)	50.8	48.0	94.5
		Mean	***98.1 ± 5.3, C.V. 5%***

(A) Processed with homogeneity/concentration verification samples from dosing prepared test day 2 (April 10, 2003).

(B) Processed with concentration verification samples from dosing prepared test day 13 (April 21, 2003).

(C) Processed with concentration verification samples from dosing prepared test day 37 (May 15, 2003).

Table II. Homogeneity and Stability of DCPD/Codimer Concentrate in Dosing Formulations

Sample Type	mg/mL DCPD/Codimer Concentrate		Percent
	Nominal	Measured	Nominal
10-Apr-2003			
Homogeneity			
CONTROL	0.00	ND(A)	----
TOP	2.5	2.70	108.0
MIDDLE	2.5	2.53	101.2
BOTTOM	2.5	2.51	100.4
	Mean(B)***:***	***2.58 ± 0.10***	***(103.2%)***
		C.V. 4%	
TOP	12.5	13.1	104.8
MIDDLE	12.5	12.5	100.0
BOTTOM	12.5	12.1	96.8
	Mean(B)***:***	***12.6 ± 0.50***	***(100.5%)***
		C.V. 4%	
TOP	50.0	49.1	98.2
MIDDLE	50.0	47.6	95.2
BOTTOM	50.0	48.4	96.8
	Mean(B)***:***	***48.4 ± 0.75***	***(96.8%)***
		C.V. 2%	
Stability(C)			
	2.5	2.50	100.0
	12.5	12.3	98.4
	50.0	50.5	101.0

(A) Denotes not detected.
(B) The average measured concentration, average percent of nominal (in parentheses and based on average measured), standard deviation, and coefficient of variation of top, middle, and bottom (mean result, n=3).
(C) Stability samples held 5 hours a room temperature.

Table III. Concentration Verification of DCPD/Codimer Concentrate in Dosing Suspensions

Sample Type	mg/mL DCPD/Codimer Concentrate		Percent
	Nominal	Measured	Nominal
21-Apr-2003 Concentration Verification			
CONTROL	0.00	ND(A)	----
#1	2.5	2.77	110.8
#2	2.5	2.73	108.2
		Mean(B)***: 2.75 ± 0.03***	***(110.0%)***
		C.V. 1%	
#1	12.5	13.5	108.0
#2	12.5	12.6	100.8
		Mean(B)***: 13.1 ± 0.64***	***(104.4%)***
		C.V. 5%	
#1	50.0-1A	53.7	107.4
	50.0-1B	52.1	104.2
		Mean(C)***: 52.9***	***(105.8%)***
#2	50.0	52.0	104.0
		Mean(D)***: 52.5 ± 0.64***	***(104.9%)***
		C.V. 1%	
15-May-2003 Concentration Verification			
CONTROL	0.00	ND(A)	----
#1	2.5	2.61	104.4
#2	2.5	2.52	100.8
		Mean(B)***: 2.57 ± 0.06***	***(102.6%)***
		C.V. 2%	
#1	12.5	13.0	104.0
#2	12.5	12.4	99.2
		Mean(B)***: 12.7 ± 0.42***	***(101.6%)***
		C.V. 3%	
#1	50.0	48.7	97.4
#2	50.0	48.2	96.4
		Mean(B)***: 48.5 ± 0.35***	***(96.9%)***
		C.V. 1%	

(A) Denotes not detected.
(B) The average measured concentration, average percent of nominal (in parentheses and based on averaged measured), standard deviation, and coefficient of variation of duplicate samples.
(C) The average measured concentration, average percent of nominal (in parentheses and based on average measured) of duplicate reanalysis of the original sample #2. Original analysis was not acceptable due to aliquot error in the analysis.
(D) The average measured concentration, average percent of nominal (in parentheses and based on average measured), standard deviation, and coefficient of variation of the average of duplicate samples including the average of duplicate reanalysis of the original sample #2.

Figure 1
Representative Analytical Calibration Curve

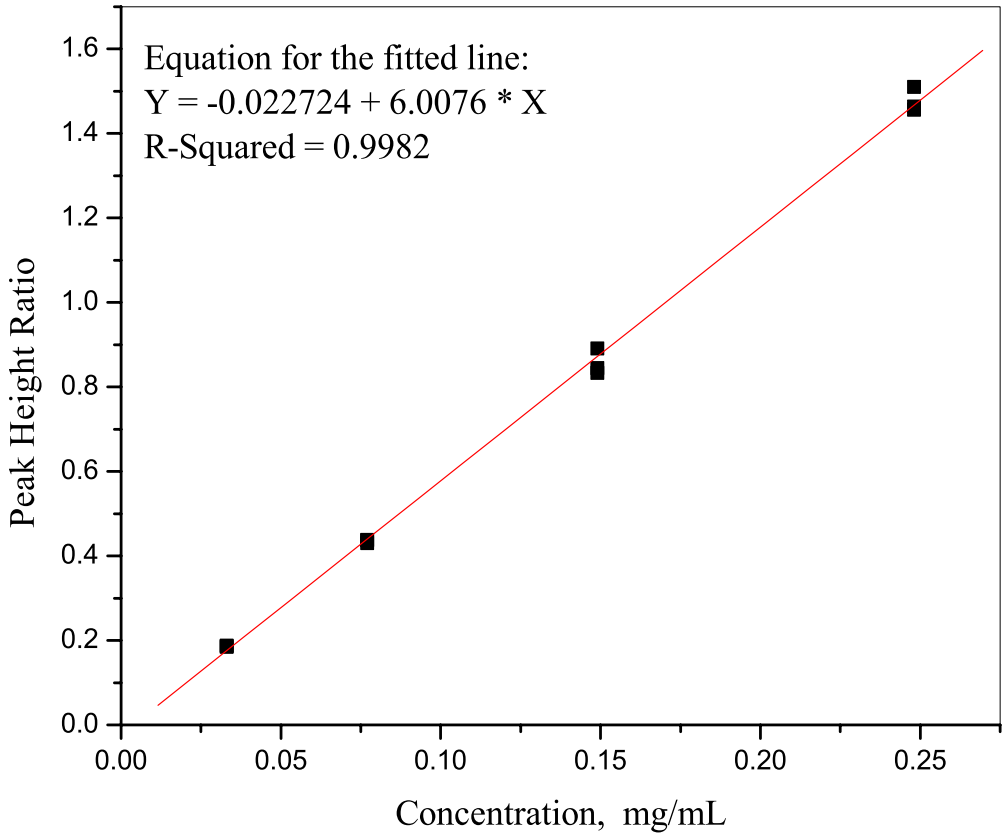


Figure 1: Calibration curve showing linear fit (line) to replicate peak height ratio (squares) for calibration solutions of DCPD/Codimer Concentrate diluted over a concentration range of 0.033 to 0.248 mg/mL.

Figure 2
Representative Gas Chromatography Chromatograms

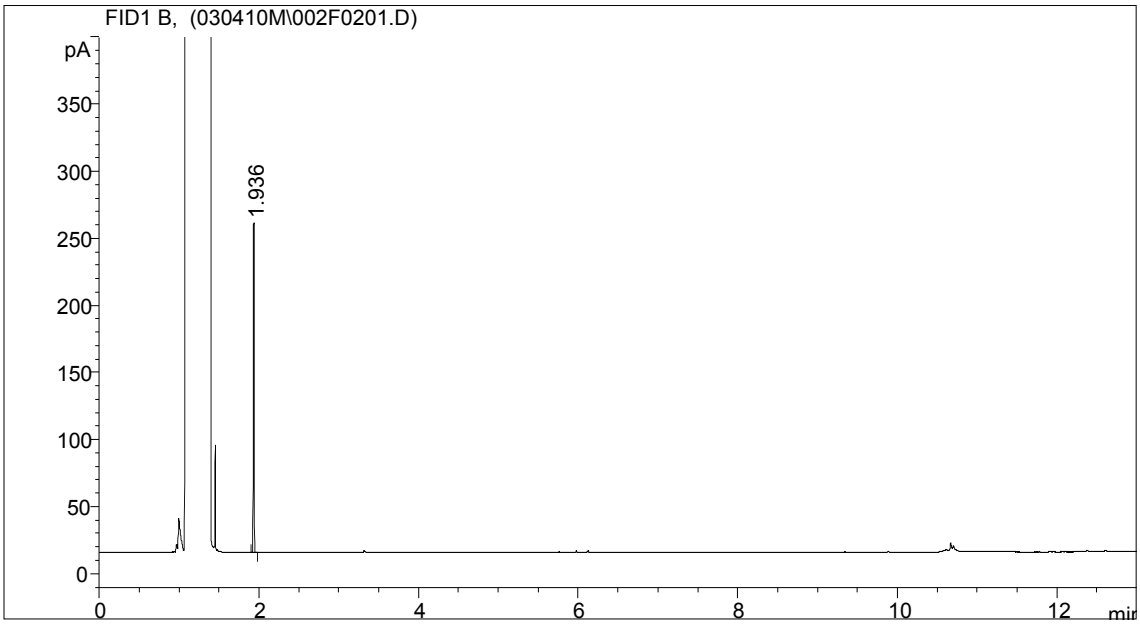


Figure 2a: Representative GC chromatogram of the 0 mg/mL (control) sample. Retention time for DCPD isomer #2 is approximately 4.0 minutes. The internal standard peak retention time is approximately 1.9 minutes.

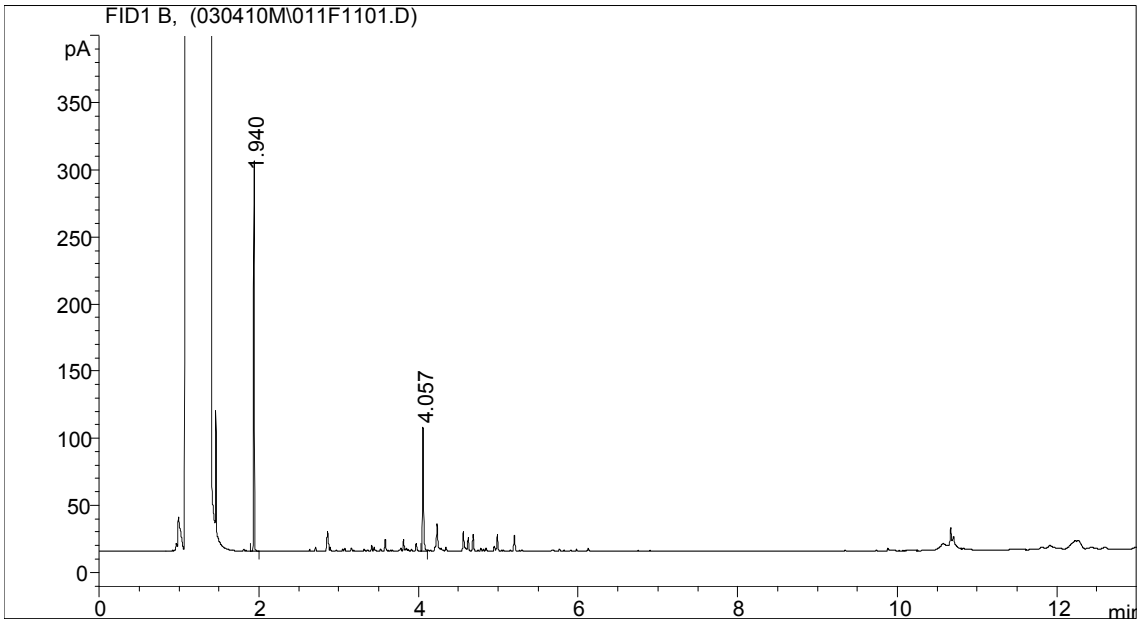


Figure 2b: Representative GC chromatogram of 2.5 mg/mL DCPD/Codimer Concentrate dosing formulation diluted to a nominal concentration of 0.06 mg/mL. The measured concentration of the representative solution is 2.50 mg/mL.

Figure 2 (continued)
Representative Gas Chromatography Chromatograms

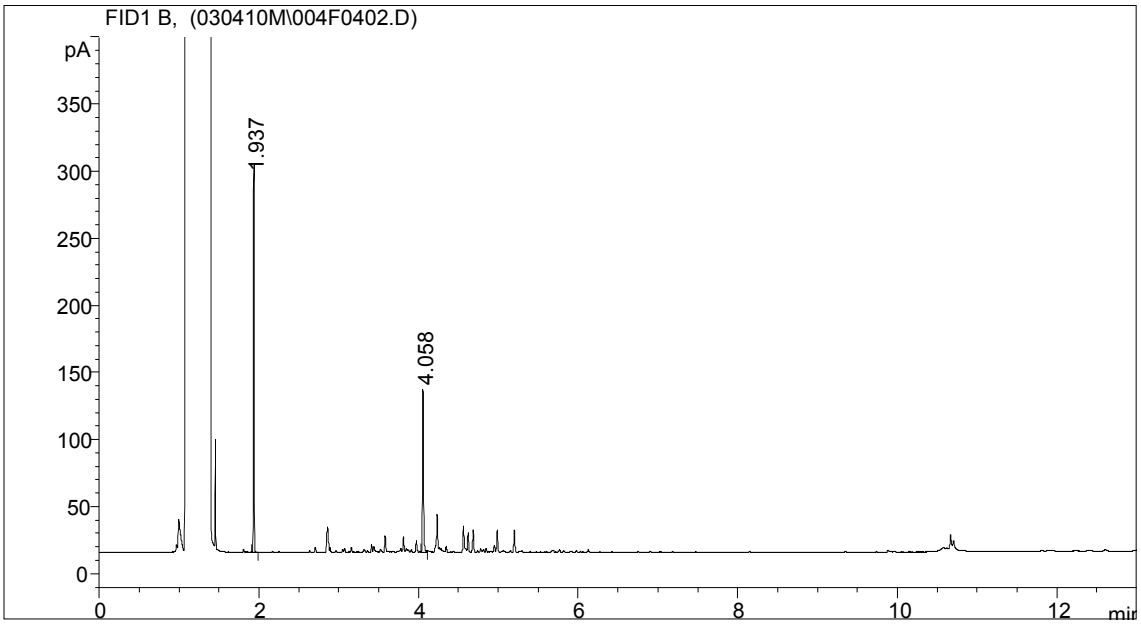


Figure 2c: Representative GC chromatogram of 0.077 mg/mL DCPD/Codimer Concentrate analytical reference solution.

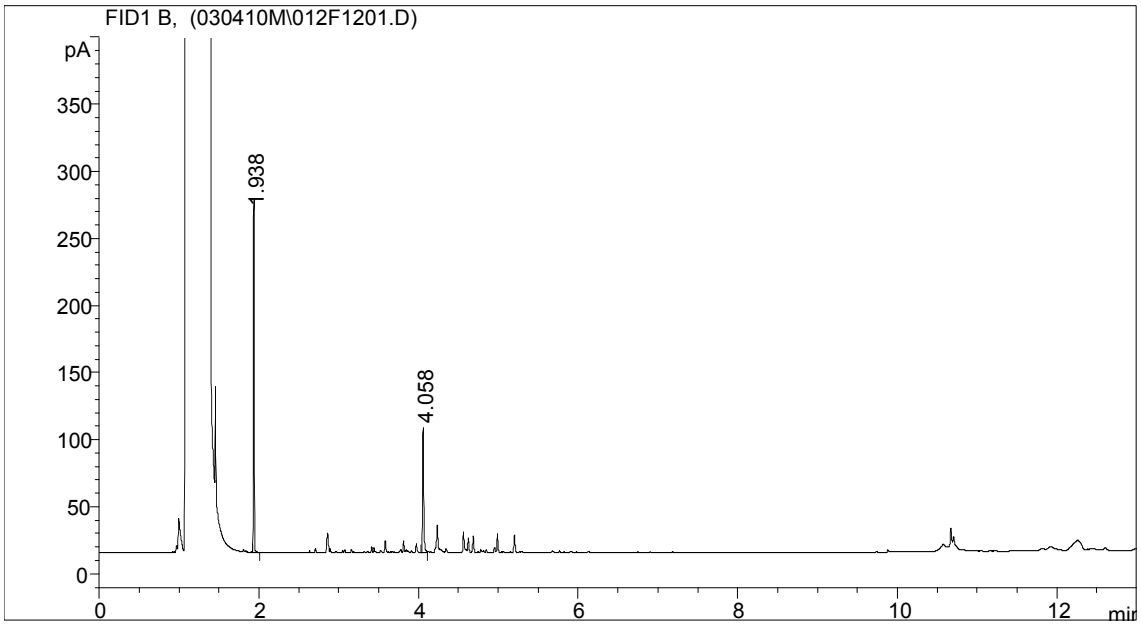


Figure 2d: Representative GC chromatogram of 2.47 mg/mL spiked dosing formulation diluted to nominal concentration of approximately 0.06 mg/mL of DCPD/Codimer Concentrate. The measured concentration of the representative solution is 2.73 mg/mL.

Pre-Study Stability Report

TEST SUBSTANCE STABILITY OF DICYCLOPENTADIENE/CODIMER CONCENTRATE (DCPD/CODIMER CONCENTRATE)

Medical Research Project Number:	5672
Haskell Sample Number:	H-25430
Analytical Report Number:	HA-2003-026

SUMMARY

At the end of the DCPD/Codimer Concentrate Developmental pilot study (MR 14294/SC840), a sample of DCPD/Codimer Concentrate was received on February 14, 2003, and analyzed February 19, 2003. The percentage of DCPD isomer #2 was measured to be 25.2% ± 0.50 with a range of 24.7 to 25.6% for replicate analyses (n = 3). Haskell Laboratory reported a component content of 28.6% (based on analysis for the DCPD isomer #2) when the DCPD/Codimer Concentrate was characterized (Dupont-11642).

SIGNATURES:

Analysis and report by: Janet C. Maslanka 28-Oct-2003
Janet C. Maslanka (Date)
Senior Staff Chemist

Date issued: 28-Oct-2003

METHODS

Analysis for the percentage of DCPD isomer #2 in a sample of DCPD/Codimer Concentrate was performed by gas chromatography (GC). This one major peak (DCPD isomer #2) in the GC analysis of the DCPD/Codimer Concentrate was used for the quantitation of the samples.

SAMPLE PREPARATION & ANALYSIS

For the analysis, aliquots (0.4688, 0.4871, 0.4858 grams) of DCPD/Codimer Concentrate were dissolved in hexane (50 mL) to give nominal concentrations of 9,376, 9,742, and 9,716 ppm. The aliquots were further diluted to a nominal concentration of 150, 156, 155 ppm, respectively, after the addition of the internal standard (refer to Calibration and Quantitation Section) and analyzed according to the method below.

INSTRUMENT & CONDITIONS

Instrument:	Hewlett-Packard Model 6890 GC
Column:	DB-1, 30 m x 0.25 mm ID, 0.25 μm film thickness
Injector:	Split, 180°C
Detector:	FID; 280°C
Carrier Gas:	Helium (2.7 mL/min)
Split ratio:	10:1
Injection Volume:	3 microliter
Oven Program:	Gradient
Initial Temperature:	50°C
Initial Time:	1.0 min.
Level 1 Rate:	20°C/min.
Level 1 Temperature:	250°C
Level 1 Time:	2.00 min.
Total run time:	13.00 min.

CALIBRATION & QUANTITATION

An analytical standard dicyclopentadiene (DCPD, 99.7% pure) was purchased from Aldrich Chemical Co., Inc. for the analysis. A stock solution was prepared in hexane. Calibration solutions of approximately 20 to 60 ppm were prepared in hexane from this solution. A stock solution of the internal standard (toluene, 99.5% pure) was prepared in hexane and added to each calibration standard and test solution to give a final concentration of approximately 30 ppm. The ratio of the peak height for DCPD isomer #2 and for the internal standard from replicate GC analysis of these solutions were used to construct a calibration curve by least squares regression. Measured concentrations for each purity solution were determined by applying the peak height ratios from replicate injections of each sample to the calibration curve.

RESULTS

DCPD/Codimer concentrate (DCPD isomer #2) eluted from the GC column as resolved peak with retention time of approximately 4.0 minutes. The peak height was used with the internal standard peak height to form a ratio for calculating the amount of DCPD/Codimer Concentrate in the test substance. Haskell Laboratory reported this component as 28.6% (based on the DCPD isomer #2 in the sample stream) when the sample was characterized (Dupont-11642).

Table 1. The percent of active ingredient (a.i.) in the DCPD co-dimer sample analyzed February 19, 2003.

	ppm DCPD co-dimer		Percent
Aliquot	Targeted	Measured	Nominal
1	150	37.0	24.7
2	156	39.9	25.6
3	155	36.5	25.5
Average Percent Nominal			**25.2**
Standard Deviation			**± 0.50**
Coefficient of Variation			**2%**

Post-Study Stability Report

TEST SUBSTANCE STABILITY OF DICYCLOPENTADIENE/CODIMER CONCENTRATE (DCPD/CODIMER CONCENTRATE)

Medical Research Project Number:	5672
Haskell Sample Number:	H-25430
Analytical Report Number:	Dupont-13129

SUMMARY

Near the end of the DCPD/Codimer Concentrate Developmental main study (MR 14294/SC1422), a sample of DCPD/Codimer Concentrate was received and analyzed on May 14, 2003. The percentage of DCPD isomer #2 was measured to be 24.7% ± 0.85 with a range of 23.9 to 25.6% for replicate analyses (n = 3). Haskell Laboratory reported a component content of 28.6% (based on analysis for the DCPD isomer #2) when the DCPD/Codimer Concentrate was characterized (Dupont-11642).

SIGNATURES:

Analysis by: Sheila A. Riley 28-Oct-2003
Sheila A. Riley
Chemistry Associate
Date

Report by: Janet C. Maslanka 28-Oct-2003
Janet C. Maslanka
Senior Staff Chemist
Date

Date issued: 28-Oct-2003

METHODS

Analysis for the percentage of DCPD isomer #2 in a sample of DCPD/Codimer Concentrate was performed by gas chromatography (GC). This one major peak (DCPD isomer #2) in the GC analysis of the DCPD/Codimer Concentrate was used for the quantitation of the samples.

SAMPLE PREPARATION & ANALYSIS

For the analysis, aliquots (0.0450, 0.0445, 0.0465 grams) of DCPD/Codimer Concentrate were dissolved in hexane (50 mL) to give nominal concentrations of 900, 890, and 930 ppm. The aliquots were further diluted to a nominal concentration of 151, 150, 149 ppm, respectively, after the addition of the internal standard (refer to Calibration and Quantitation Section) and analyzed according to the method below.

INSTRUMENT & CONDITIONS

Instrument:	Hewlett-Packard Model 6890 GC
Column:	DB-1, 30 m x 0.25 mm ID, 0.25 μm film thickness
Injector:	Split, 180°C
Detector:	FID; 280°C
Carrier Gas:	Helium (2.7 mL/min)
Split ratio:	10:1
Injection Volume:	3 microliter
Oven Program:	Gradient
Initial Temperature:	50°C
Initial Time:	1.0 min.
Level 1 Rate:	20°C/min.
Level 1 Temperature:	250°C
Level 1 Time:	2.00 min.
Total run time:	13.00 min.

CALIBRATION & QUANTITATION

An analytical standard dicyclopentadiene (DCPD, 99.7% pure) was purchased from Aldrich Chemical Co., Inc. for the analysis. A stock solution was prepared in hexane. Calibration solutions of approximately 20 to 60 ppm were prepared in hexane from this solution. A stock solution of the internal standard (toluene, 99.5% pure) was prepared in hexane and added to each calibration standard and test solution to give a final concentration of approximately 30 ppm. The ratio of the peak height for DCPD isomer #2 and for the internal standard from replicate GC analysis of these solutions were used to construct a calibration curve by least squares regression. Measured concentrations for each purity solution were determined by applying the peak height ratios from replicate injections of each sample to the calibration curve.

Dupont-13129 page 3 of 3

RESULTS

DCPD/Codimer concentrate (DCPD isomer #2) eluted from the GC column as resolved peak with retention time of approximately 4.0 minutes. The peak height was used with the internal standard peak height to form a ratio for calculating the amount of DCPD/Codimer Concentrate in the test substance. Haskell Laboratory reported this component as 28.6% (based on the DCPD isomer #2 in the sample stream) when the sample was characterized (Dupont-11642).

Table 1. The percent of active ingredient (a.i.) in the DCPD co-dimer sample analyzed May 14, 2003.

	ppm DCPD co-dimer		Percent
Aliquot	Targeted	Measured	Nominal
1	151	38.7	25.6
2	150	35.9	23.9
3	149	36.7	24.6
Average Percent Nominal			**24.7**
Standard Deviation			**± 0.85**
Coefficient of Variation			**3%**

Individual Clinical Observations and Mortality Data in Subchronic Male Rats

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-29 = Cohabitation period

Postdosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (PREDOSING)

GROUP: I CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671670	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671677	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671679	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671688	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671690	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671697	ALOPECIA BOTH FRONT PAW(S)	9	30
	SACRIFICED BY DESIGN TEST DAY 30		
671709	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671710	ALOPECIA BOTH FRONT PAW(S)	6	30
	SACRIFICED BY DESIGN TEST DAY 30		
671712	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671713	ALOPECIA BOTH FRONT PAW(S)	10	30
	SORE LEFT FRONT PAW(S)	14	30
	SACRIFICED BY DESIGN TEST DAY 30		
671719	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671720	ALOPECIA BOTH FRONT PAW(S)	2	30
	ALOPECIA ABDOMEN	4	5
	ALOPECIA LEFT SIDE(S)	6	23
	ALOPECIA LEFT REAR LEG(S)	7	26
	ALOPECIA BOTH FRONT LEG(S)	15	30
	ALOPECIA ABDOMEN	18	30
	ALOPECIA LEFT HIND QUARTERS	18	20
	SACRIFICED BY DESIGN TEST DAY 30		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (PREDOSING)

GROUP: III CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671673	ALOPECIA BOTH FRONT PAW(S)	3	30
	ALOPECIA BOTH FRONT LEG(S)	4	30
	SACRIFICED BY DESIGN TEST DAY 30		
671674	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671694	ALOPECIA BOTH FRONT PAW(S)	15	30
	SACRIFICED BY DESIGN TEST DAY 30		
671695	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671696	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671698	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671700	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671704	ALOPECIA BOTH FRONT PAW(S)	14	30
	ALOPECIA BOTH FRONT LEG(S)	19	30
	SACRIFICED BY DESIGN TEST DAY 30		
671714	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671721	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671723	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671724	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (PREDOSING)

GROUP: V CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671671	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671672	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671675	ALOPECIA BOTH FRONT PAW(S)	22	30
	SACRIFICED BY DESIGN TEST DAY 30		
671680	ALOPECIA BOTH FRONT PAW(S)	15	30
	ALOPECIA BOTH FRONT LEG(S)	24	30
	SACRIFICED BY DESIGN TEST DAY 30		
671682	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671683	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671684	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671685	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671689	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671705	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671718	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671725	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (PREDOSING)

GROUP: VII CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671678	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671686	ALOPECIA BOTH FRONT PAW(S)	14	16
	ALOPECIA LEFT FRONT PAW(S)	17	17
	ALOPECIA BOTH FRONT PAW(S)	18	30
	SACRIFICED BY DESIGN TEST DAY 30		
671687	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671691	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671692	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671693	ALOPECIA BOTH FRONT PAW(S)	15	26
	SACRIFICED BY DESIGN TEST DAY 30		
671699	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671702	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671706	ALOPECIA BOTH FRONT PAW(S)	9	27
	ALOPECIA BOTH FRONT LEG(S)	17	26
	ALOPECIA LEFT FRONT LEG(S)	28	30
	SACRIFICED BY DESIGN TEST DAY 30		
671708	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671711	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 30		
671722	ALOPECIA BOTH FRONT PAW(S)	10	30
	ALOPECIA BOTH FRONT LEG(S)	15	30
	SACRIFICED BY DESIGN TEST DAY 30		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (POSTDOSING)

GROUP: I CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671670	-		
671677	-		
671679	-		
671688	-		
671690	-		
671697	-		
671709	-		
671710	-		
671712	-		
671713	-		
671719	-		
671720	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (POSTDOSING)

GROUP: III CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671673	-		
671674	-		
671694	-		
671695	-		
671696	-		
671698	-		
671700	-		
671704	-		
671714	-		
671721	-		
671723	-		
671724	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (POSTDOSING)

GROUP: V CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671671	-		
671672	-		
671675	-		
671680	-		
671682	-		
671683	-		
671684	-		
671685	-		
671689	-		
671705	-		
671718	-		
671725	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC MALE RATS (POSTDOSING)

GROUP: VII CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671678	-		
671686	-		
671687	COLORED DISCHARGE RIGHT EYE(S) RED	16	16
671691	-		
671692	-		
671693	-		
671699	-		
671702	-		
671706	-		
671708	-		
671711	-		
671722	-		

Individual Detailed Clinical Observations in Subchronic Male Rats

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-29 = Cohabitation period

Detailed clinical observations were conducted during the pretest period and on test days 8, 15, 22, and 29.

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

GROUP: I CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671670	NO ABNORMALITIES DETECTED		
672677	NO ABNORMALITIES DETECTED		
671679	NO ABNORMALITIES DETECTED		
671688	NO ABNORMALITIES DETECTED		
671690	NO ABNORMALITIES DETECTED		
671697	ALOPECIA BOTH FRONT PAW(S)	15	29
671709	NO ABNORMALITIES DETECTED		
671710	ALOPECIA BOTH FRONT PAW(S)	8	29
671712	NO ABNORMALITIES DETECTED		
671713	ALOPECIA BOTH FRONT PAW(S)	-2	29
	SORE LEFT FRONT PAW(S)	15	29
671719	NO ABNORMALITIES DETECTED		
671720	ALOPECIA BOTH FRONT PAW(S)	-2	29
	ALOPECIA BOTH FRONT LEGS(S)	-2	-2
	ALOPECIA LEFT SIDE(S)	8	22
	ALOPECIA LEFT REAR LEG(S)	8	22
	ALOPECIA BOTH FRONT LEG(S)	15	29
	ALOPECIA ABDOMEN	22	29

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

GROUP: III CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671673	ALOPECIA BOTH FRONT PAW(S)	-2	29
	ALOPECIA BOTH FRONT LEG(S)	-2	29
671674	NO ABNORMALITIES DETECTED		
671694	ALOPECIA BOTH FRONT PAW(S)	15	29
671695	NO ABNORMALITIES DETECTED		
671696	NO ABNORMALITIES DETECTED		
671698	NO ABNORMALITIES DETECTED		
671700	NO ABNORMALITIES DETECTED		
671704	ALOPECIA BOTH FRONT PAW(S)	15	29
	ALOPECIA BOTH FRONT LEG(S)	22	29
671714	NO ABNORMALITIES DETECTED		
671721	NO ABNORMALITIES DETECTED		
671723	NO ABNORMALITIES DETECTED		
671724	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

GROUP: V CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671671	NO ABNORMALITIES DETECTED		
671672	NO ABNORMALITIES DETECTED		
671675	ALOPECIA BOTH FRONT PAW(S)	22	29
671680	ALOPECIA BOTH FRONT PAW(S)	15	29
	ALOPECIA BOTH FRONT LEG(S)	29	29
671682	NO ABNORMALITIES DETECTED		
671683	NO ABNORMALITIES DETECTED		
671684	NO ABNORMALITIES DETECTED		
671685	NO ABNORMALITIES DETECTED		
671689	NO ABNORMALITIES DETECTED		
671705	NO ABNORMALITIES DETECTED		
671718	NO ABNORMALITIES DETECTED		
671725	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC MALE RATS

GROUP: VII CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671678	NO ABNORMALITIES DETECTED		
671686	ALOPECIA BOTH FRONT PAW(S)	15	29
671687	NO ABNORMALITIES DETECTED		
671691	NO ABNORMALITIES DETECTED		
671692	NO ABNORMALITIES DETECTED		
671693	ALOPECIA BOTH FRONT PAW(S)	15	22
671699	NO ABNORMALITIES DETECTED		
671702	NO ABNORMALITIES DETECTED		
671706	ALOPECIA BOTH FRONT PAW(S)	15	22
	ALOPECIA BOTH FRONT LEG(S)	22	22
	ALOPECIA LEFT FRONT LEG(S)	29	29
671708	NO ABNORMALITIES DETECTED		
671711	NO ABNORMALITIES DETECTED		
671722	ALOPECIA BOTH FRONT PAW(S)	15	29
	ALOPECIA BOTH FRONT LEG(S)	15	29

Individual Clinical Observations and Mortality Data in Subchronic Female Rats

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS

EXPLANATORY NOTES

Notes

Postdosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS (PREDOSING)

GROUP: II CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671747	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671758	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671766	ALOPECIA BOTH FRONT PAW(S)	15	20
	ALOPECIA BOTH FRONT LEG(S)	15	20
	SACRIFICED BY DESIGN TEST DAY 31		
671770	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671794	ALOPECIA BOTH FRONT PAW(S)	15	20
	ALOPECIA BOTH FRONT LEG(S)	17	20
	ALOPECIA BOTH FRONT PAW(S)	23	24
	ALOPECIA BOTH FRONT PAW(S)	28	31
	SACRIFICED BY DESIGN TEST DAY 31		
671799	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671808	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671810	ALOPECIA BOTH FRONT PAW(S)	6	24
	ALOPECIA BOTH FRONT LEG(S)	9	31
	ALOPECIA LEFT SHOULDER(S)	24	31
	SACRIFICED BY DESIGN TEST DAY 31		
671824	ALOPECIA LEFT SIDE(S)	9	16
	ALOPECIA BOTH FRONT LEG(S)	14	20
	ALOPECIA ABDOMEN	17	31
	ALOPECIA PERINEUM	18	22
	ALOPECIA LEFT FRONT LEG(S)	21	24
	ALOPECIA BOTH FRONT LEG(S)	25	31
	ALOPECIA PERINEUM	25	31
	SACRIFICED BY DESIGN TEST DAY 31		
671828	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671834	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671836	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS (PREDOSING)

GROUP: IV CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671727	ALOPECIA BOTH FRONT PAW(S)	23	31
	SACRIFICED BY DESIGN TEST DAY 31		
671733	ALOPECIA BOTH FRONT PAW(S)	1	31
	ALOPECIA LEFT FRONT LEG(S)	6	8
	ALOPECIA BOTH FRONT LEG(S)	9	31
	ALOPECIA LEFT SHOULDER(S)	13	31
	ALOPECIA LEFT SIDE(S)	13	31
	SACRIFICED BY DESIGN TEST DAY 31		
671737	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671742	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671761	ALOPECIA RIGHT FRONT PAW(S)	18	23
	SACRIFICED BY DESIGN TEST DAY 31		
671768	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671783	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671788	ALOPECIA RIGHT FRONT PAW(S)	18	22
	ALOPECIA BOTH FRONT LEG(S)	18	22
	SACRIFICED BY DESIGN TEST DAY 31		
671800	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671812	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671815	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671825	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS (PREDOSING)

GROUP: VI CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671730	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671739	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671772	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671790	ALOPECIA RIGHT FRONT LEG(S)	17	31
	SACRIFICED BY DESIGN TEST DAY 31		
671806	ALOPECIA BOTH FRONT PAW(S)	14	31
	ALOPECIA BOTH FRONT LEG(S)	17	31
	SACRIFICED BY DESIGN TEST DAY 31		
671814	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671816	SORE RIGHT REAR LEG(S)	3	24
	SACRIFICED BY DESIGN TEST DAY 31		
671826	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671831	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671832	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671835	ALOPECIA BOTH FRONT PAW(S)	17	29
	ALOPECIA ABDOMEN	27	31
	SACRIFICED BY DESIGN TEST DAY 31		
671838	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS (PREDOSING)

GROUP: VIII CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671735	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671741	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671748	(EAR SHAKE)	9	9
	ALOPECIA BOTH FRONT LEG(S)	10	31
	(EAR SHAKE)	21	21
	SACRIFICED BY DESIGN TEST DAY 31		
671756	ALOPECIA BOTH FRONT PAW(S)	10	23
	ALOPECIA BOTH FRONT LEG(S)	17	23
	ALOPECIA LEFT FRONT LEG(S)	24	26
	ALOPECIA BOTH FRONT LEG(S)	27	31
	SACRIFICED BY DESIGN TEST DAY 31		
671762	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671763	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671767	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671778	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671793	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671797	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		
671811	ALOPECIA BOTH FRONT LEG(S)	10	31
	ALOPECIA BOTH FRONT PAW(S)	19	31
	SACRIFICED BY DESIGN TEST DAY 31		
671820	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 31		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS (POSTDOSING)

GROUP: II CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER		OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671747	-			
671758	-			
671766	-			
671770	-			
671794	-			
671799	-			
671808	-			
671810	-			
671824	-			
671828	-			
671834	-			
671836	-			

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS (POSTDOSING)

GROUP: IV CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671727	-		
671733	-		
671737	-		
671742	-		
671761	-		
671768	-		
671783	-		
671788	-		
671800	-		
671812	-		
671815	-		
671825	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS (POSTDOSING)

GROUP: VI CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671730	-		
671739	-		
671772	-		
671790	-		
671806	-		
671814	-		
671816	-		
671826	-		
671831	-		
671832	-		
671835	-		
671838	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SUBCHRONIC FEMALE RATS (POSTDOSING)

GROUP: VIII CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671735	-		
671741	-		
671748	-		
671756	-		
671762	-		
671763	-		
671767	-		
671778	-		
671793	-		
671797	-		
671811	-		
671820	-		

Individual Detailed Clinical Observations in Subchronic Female Rats

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS

EXPLANATORY NOTES

Notes

Detailed clinical observations were conducted during the pretest period and on test days 8, 15, 22, and 29.

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN
SUBCHRONIC FEMALE RATS

GROUP: II CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671747	NO ABNORMALITIES DETECTED		
671758	NO ABNORMALITIES DETECTED		
671766	ALOPECIA BOTH FRONT PAW(S)	15	15
	ALOPECIA BOTH FRONT LEG(S)	15	15
671770	NO ABNORMALITIES DETECTED		
671794	ALOPECIA BOTH FRONT PAW(S)	15	15
	ALOPECIA BOTH FRONT PAW(S)	29	29
671799	NO ABNORMALITIES DETECTED		
671808	NO ABNORMALITIES DETECTED		
671810	ALOPECIA BOTH FRONT PAW(S)	8	22
	ALOPECIA BOTH FRONT LEG(S)	15	29
	ALOPECIA LEFT SHOULDER(S)	29	29
671824	ALOPECIA LEFT SIDE(S)	15	15
	ALOPECIA BOTH FRONT LEG(S)	15	15
	ALOPECIA ABDOMEN	22	29
	ALOPECIA LEFT FRONT LEG(S)	22	29
	ALOPECIA PERINEUM	22	29
671828	NO ABNORMALITIES DETECTED		
671834	NO ABNORMALITIES DETECTED		
671836	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN
SUBCHRONIC FEMALE RATS

GROUP: IV CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671727	ALOPECIA BOTH FRONT PAW(S)	29	29
671733	ALOPECIA BOTH FRONT LEG(S)	-2	-2
	ALOPECIA BOTH FRONT PAW(S)	8	29
	ALOPECIA LEFT FRONT LEG(S)	8	8
	ALOPECIA BOTH FRONT LEG(S)	15	29
	ALOPECIA LEFT SHOULDER(S)	15	29
	ALOPECIA LEFT SIDE(S)	15	29
671737	NO ABNORMALITIES DETECTED		
671742	NO ABNORMALITIES DETECTED		
671761	ALOPECIA RIGHT FRONT PAW(S)	22	22
671768	NO ABNORMALITIES DETECTED		
671783	NO ABNORMALITIES DETECTED		
671788	ALOPECIA RIGHT FRONT PAW(S)	22	22
	ALOPECIA BOTH FRONT LEG(S)	22	22
671800	NO ABNORMALITIES DETECTED		
671812	NO ABNORMALITIES DETECTED		
671815	NO ABNORMALITIES DETECTED		
671825	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN
SUBCHRONIC FEMALE RATS

GROUP: VI CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671730	NO ABNORMALITIES DETECTED		
671739	NO ABNORMALITIES DETECTED		
671772	NO ABNORMALITIES DETECTED		
671790	ALOPECIA RIGHT FRONT LEG(S)	22	29
671806	ALOPECIA BOTH FRONT PAW(S)	15	29
	ALOPECIA BOTH FRONT LEG(S)	22	29
671814	NO ABNORMALITIES DETECTED		
671816	SORE RIGHT REAR LEG(S)	8	22
671826	NO ABNORMALITIES DETECTED		
671831	NO ABNORMALITIES DETECTED		
671832	NO ABNORMALITIES DETECTED		
671835	ALOPECIA BOTH FRONT PAW(S)	22	29
	ALOPECIA ABDOMEN	29	29
671838	NO ABNORMALITIES DETECTED		

INDIVIDUAL DETAILED CLINICAL OBSERVATIONS IN SUBCHRONIC FEMALE RATS

GROUP: VIII CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671735	NO ABNORMALITIES DETECTED		
671741	NO ABNORMALITIES DETECTED		
671748	ALOPECIA BOTH FRONT LEG(S)	15	29
671756	ALOPECIA BOTH FRONT PAW(S)	15	22
	ALOPECIA BOTH FRONT LEG(S)	22	29
671762	NO ABNORMALITIES DETECTED		
671763	NO ABNORMALITIES DETECTED		
671767	NO ABNORMALITIES DETECTED		
671778	NO ABNORMALITIES DETECTED		
671793	NO ABNORMALITIES DETECTED		
671797	NO ABNORMALITIES DETECTED		
671811	ALOPECIA BOTH FRONT LEG(S)	15	29
	ALOPECIA BOTH FRONT PAW(S)	22	29
671820	NO ABNORMALITIES DETECTED		

Individual Body Weights and Body Weight Gains of Subchronic Male Rats

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS
OF SUBCHRONIC MALE RATS

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-29 = Cohabitation period

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

GROUP: I CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29
ANIMAL #	MEAN BODY WEIGHT (grams)				
671670	274.4	322.6	368.9	402.8	445.0
671677	254.4	305.9	344.5	384.9	428.4
671679	251.1	297.0	343.8	371.2	403.3
671688	275.8	328.1	373.8	403.0	434.1
671690	261.4	315.2	360.0	413.9	434.3
671697	266.7	314.8	346.1	375.4	391.7
671709	261.2	308.0	354.4	382.7	410.7
671710	263.9	310.8	355.3	397.6	435.4
671712	273.9	326.8	374.4	399.8	430.8
671713	260.0	297.7	328.5	348.6	371.4
671719	252.4	311.7	359.7	407.7	445.9
671720	279.7	322.4	375.2	419.3	458.2

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
671670	48.2	46.3	33.9	42.2	170.6
671677	51.5	38.6	40.4	43.5	174.0
671679	45.9	46.8	27.4	32.1	152.2
671688	52.3	45.7	29.2	31.1	158.3
671690	53.8	44.8	53.9	20.4	172.9
671697	48.1	31.3	29.3	16.3	125.0
671709	46.8	46.4	28.3	28.0	149.5
671710	46.9	44.5	42.3	37.8	171.5
671712	52.9	47.6	25.4	31.0	156.9
671713	37.7	30.8	20.1	22.8	111.4
671719	59.3	48.0	48.0	38.2	193.5
671720	42.7	52.8	44.1	38.9	178.5

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

GROUP: III CONCENTRATION: 5 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29
ANIMAL #	MEAN BODY WEIGHT (grams)				
671673	282.7	344.0	401.6	430.5	478.3
671674	255.3	309.9	355.8	389.3	410.7
671694	275.3	339.4	385.6	423.8	464.2
671695	277.0	338.3	389.0	423.6	469.0
671696	270.8	324.0	375.9	398.3	443.9
671698	258.0	317.3	353.6	396.4	435.8
671700	286.4	352.2	399.9	441.2	487.4
671704	275.7	337.1	396.2	442.8	485.3
671714	263.9	315.0	358.1	395.3	436.3
671721	253.6	298.3	341.6	375.4	418.3
671723	269.1	336.9	396.5	441.7	494.9
671724	259.7	315.0	354.4	398.3	437.4

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
671673	61.3	57.6	28.9	47.8	195.6
671674	54.6	45.9	33.5	21.4	155.4
671694	64.1	46.2	38.2	40.4	188.9
671695	61.3	50.7	34.6	45.4	192.0
671696	53.2	51.9	22.4	45.6	173.1
671698	59.3	36.3	42.8	39.4	177.8
671700	65.8	47.7	41.3	46.2	201.0
671704	61.4	59.1	46.6	42.5	209.6
671714	51.1	43.1	37.2	41.0	172.4
671721	44.7	43.3	33.8	42.9	164.7
671723	67.8	59.6	45.2	53.2	225.8
671724	55.3	39.4	43.9	39.1	177.7

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

GROUP: V CONCENTRATION: 25 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29
ANIMAL #	MEAN BODY WEIGHT (grams)				
671671	247.1	297.1	341.1	368.8	401.5
671672	268.3	319.2	374.8	415.9	446.7
671675	271.9	323.1	380.1	419.6	460.9
671680	265.8	314.9	360.5	397.9	428.2
671682	260.2	328.0	382.2	429.6	465.2
671683	271.0	323.1	362.0	397.0	435.2
671684	253.7	305.8	347.9	388.1	423.0
671685	259.0	315.2	357.9	389.7	430.2
671689	277.4	336.3	395.5	441.3	487.0
671705	263.8	325.6	373.1	415.2	457.1
671718	255.9	277.2	342.5	373.9	422.9
671725	264.8	320.4	360.9	403.9	451.1

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
671671	50.0	44.0	27.7	32.7	154.4
671672	50.9	55.6	41.1	30.8	178.4
671675	51.2	57.0	39.5	41.3	189.0
671680	49.1	45.6	37.4	30.3	162.4
671682	67.8	54.2	47.4	35.6	205.0
671683	52.1	38.9	35.0	38.2	164.2
671684	52.1	42.1	40.2	34.9	169.3
671685	56.2	42.7	31.8	40.5	171.2
671689	58.9	59.2	45.8	45.7	209.6
671705	61.8	47.5	42.1	41.9	193.3
671718	21.3	65.3	31.4	49.0	167.0
671725	55.6	40.5	43.0	47.2	186.3

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC MALE RATS

GROUP: VII CONCENTRATION: 100 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29
ANIMAL #	MEAN BODY WEIGHT (grams)				
671678	256.4	302.6	347.5	388.1	427.1
671686	262.5	322.6	365.6	402.0	439.7
671687	263.8	308.4	350.4	378.9	402.9
671691	259.9	319.8	363.8	409.6	451.7
671692	274.2	317.0	351.7	388.5	417.6
671693	237.0	293.2	334.8	378.2	415.4
671699	253.8	309.1	353.9	390.9	429.0
671702	270.8	333.5	380.1	414.8	445.4
671706	269.9	330.8	378.1	424.1	466.4
671708	259.5	314.8	358.5	403.1	438.9
671711	261.5	310.4	353.5	387.7	411.6
671722	286.2	349.9	406.4	445.0	490.8

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
671678	46.2	44.9	40.6	39.0	170.7
671686	60.1	43.0	36.4	37.7	177.2
671687	44.6	42.0	28.5	24.0	139.1
671691	59.9	44.0	45.8	42.1	191.8
671692	42.8	34.7	36.8	29.1	143.4
671693	56.2	41.6	43.4	37.2	178.4
671699	55.3	44.8	37.0	38.1	175.2
671702	62.7	46.6	34.7	30.6	174.6
671706	60.9	47.3	46.0	42.3	196.5
671708	55.3	43.7	44.6	35.8	179.4
671711	48.9	43.1	34.2	23.9	150.1
671722	63.7	56.5	38.6	45.8	204.6

Individual Body Weights and Body Weight Gains of Subchronic Female Rats

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

GROUP: II CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29
ANIMAL #	MEAN BODY WEIGHT (grams)				
671747	181.9	199.7	226.8	240.8	255.0
671758	188.8	224.9	239.1	253.1	268.0
671766	187.6	199.4	203.8	213.3	237.2
671770	189.8	190.7	222.8	218.9	258.3
671794	187.6	213.2	239.3	250.3	267.0
671799	194.1	207.7	244.9	237.6	253.3
671808	200.1	211.5	218.6	236.3	251.9
671810	199.1	219.7	236.5	238.6	252.2
671824	202.8	225.6	230.2	254.7	281.6
671828	173.6	187.0	198.1	210.5	219.1
671834	194.3	204.7	222.6	231.5	238.6
671836	179.1	193.0	209.5	223.3	234.9

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
671747	17.8	27.1	14.0	14.2	73.1
671758	36.1	14.2	14.0	14.9	79.2
671766	11.8	4.4	9.5	23.9	49.6
671770	0.9	32.1	-3.9	39.4	68.5
671794	25.6	26.1	11.0	16.7	79.4
671799	13.6	37.2	-7.3	15.7	59.2
671808	11.4	7.1	17.7	15.6	51.8
671810	20.6	16.8	2.1	13.6	53.1
671824	22.8	4.6	24.5	26.9	78.8
671828	13.4	11.1	12.4	8.6	45.5
671834	10.4	17.9	8.9	7.1	44.3
671836	13.9	16.5	13.8	11.6	55.8

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

GROUP: IV CONCENTRATION: 5 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29
ANIMAL #	MEAN BODY WEIGHT (grams)				
671727	172.0	183.8	201.4	208.3	219.8
671733	204.4	218.9	225.8	234.4	250.3
671737	184.8	208.1	227.9	239.7	249.5
671742	205.6	232.0	240.3	271.0	287.1
671761	193.7	209.5	226.4	245.9	284.0
671768	203.1	218.7	239.7	239.8	264.0
671783	198.2	224.0	232.3	264.9	282.2
671788	191.5	192.9	213.4	228.6	242.0
671800	190.6	211.5	220.4	241.2	233.1
671812	177.9	192.2	207.5	223.6	226.0
671815	183.0	183.7	207.4	221.4	230.4
671825	207.6	211.8	244.0	258.0	279.0

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
671727	11.8	17.6	6.9	11.5	47.8
671733	14.5	6.9	8.6	15.9	45.9
671737	23.3	19.8	11.8	9.8	64.7
671742	26.4	8.3	30.7	16.1	81.5
671761	15.8	16.9	19.5	38.1	90.3
671768	15.6	21.0	0.1	24.2	60.9
671783	25.8	8.3	32.6	17.3	84.0
671788	1.4	20.5	15.2	13.4	50.5
671800	20.9	8.9	20.8	-8.1	42.5
671812	14.3	15.3	16.1	2.4	48.1
671815	0.7	23.7	14.0	9.0	47.4
671825	4.2	32.2	14.0	21.0	71.4

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

GROUP: VI CONCENTRATION: 25 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29
ANIMAL #	MEAN BODY WEIGHT (grams)				
671730	212.2	218.3	251.0	277.6	285.2
671739	184.7	199.1	208.8	225.8	240.4
671772	194.2	217.0	237.3	258.2	248.6
671790	191.2	200.3	214.0	222.8	233.6
671806	192.6	210.8	223.0	238.0	253.9
671814	191.7	205.0	217.4	223.4	236.4
671816	179.7	179.4	198.8	211.1	217.1
671826	178.4	192.4	224.0	246.6	259.6
671831	195.2	205.6	213.8	223.1	242.3
671832	192.5	194.7	215.8	229.1	235.4
671835	205.5	214.9	244.2	263.9	271.1
671838	179.5	189.1	200.4	202.2	214.5

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
671730	6.1	32.7	26.6	7.6	73.0
671739	14.4	9.7	17.0	14.6	55.7
671772	22.8	20.3	20.9	-9.6	54.4
671790	9.1	13.7	8.8	10.8	42.4
671806	18.2	12.2	15.0	15.9	61.3
671814	13.3	12.4	6.0	13.0	44.7
671816	-0.3	19.4	12.3	6.0	37.4
671826	14.0	31.6	22.6	13.0	81.2
671831	10.4	8.2	9.3	19.2	47.1
671832	2.2	21.1	13.3	6.3	42.9
671835	9.4	29.3	19.7	7.2	65.6
671838	9.6	11.3	1.8	12.3	35.0

INDIVIDUAL BODY WEIGHTS AND BODY WEIGHT GAINS (grams) OF SUBCHRONIC FEMALE RATS

GROUP: VIII CONCENTRATION: 100 MG/KG/DAY

DAYS ON TEST:	1	8	15	22	29
ANIMAL #	MEAN BODY WEIGHT (grams)				
671735	190.0	197.4	202.0	213.3	221.7
671741	194.1	207.3	221.3	229.3	232.5
671748	197.1	215.7	232.8	233.5	233.4
671756	186.3	188.3	201.6	210.5	224.8
671762	190.0	221.7	232.2	252.9	265.9
671763	182.5	191.7	202.6	222.9	243.1
671767	191.1	194.2	204.2	228.8	237.7
671778	179.5	185.4	205.8	219.5	217.4
671793	192.5	190.6	209.6	223.4	241.3
671797	207.5	218.1	226.3	241.6	261.9
671811	196.8	206.1	237.5	248.5	259.3
671820	206.7	226.4	227.5	249.3	253.9

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #	MEAN BODY WEIGHT GAINS (grams)				
671735	7.4	4.6	11.3	8.4	31.7
671741	13.2	14.0	8.0	3.2	38.4
671748	18.6	17.1	0.7	-0.1	36.3
671756	2.0	13.3	8.9	14.3	38.5
671762	31.7	10.5	20.7	13.0	75.9
671763	9.2	10.9	20.3	20.2	60.6
671767	3.1	10.0	24.6	8.9	46.6
671778	5.9	20.4	13.7	-2.1	37.9
671793	-1.9	19.0	13.8	17.9	48.8
671797	10.6	8.2	15.3	20.3	54.4
671811	9.3	31.4	11.0	10.8	62.5
671820	19.7	1.1	21.8	4.6	47.2

Individual Food Consumption by Subchronic Male Rats During Premating

INDIVIDUAL FOOD CONSUMPTION BY SUBCHRONIC MALE RATS
DURING PREMATING

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating period
Test Days 15-29 = Cohabitation period

Food consumption was not determined during or following the cohabitation period.

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC MALE RATS DURING PREMATING

GROUP: I CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #			
671670	25.1	27.4	26.3
671677	26.4	28.2	27.3
671679	24.5	25.7	25.1
671688	26.6	28.0	27.3
671690	25.4	26.8	26.1
671697	28.2	26.1	27.2
671709	24.1	25.9	25.0
671710	25.8	30.0	27.9
671712	27.4	39.1	33.2
671713	23.9	24.0	23.9
671719	26.6	28.2	27.4
671720	26.8	28.4	27.6

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC MALE RATS DURING PREMATING

GROUP: III CONCENTRATION: 5 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #			
671673	29.0	30.4	29.7
671674	25.8	28.5	27.2
671694	31.9	30.8	31.3
671695	28.7	29.4	29.0
671696	28.7	30.5	29.6
671698	27.5	27.1	27.3
671700	29.4	29.4	29.4
671704	27.8	29.7	28.7
671714	26.9	27.8	27.4
671721	26.7	27.1	26.9
671723	27.8	32.1	29.9
671724	27.4	28.8	28.1

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC MALE RATS DURING PREMATING

GROUP: V CONCENTRATION: 25 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #			
671671	25.6	26.2	25.9
671672	23.6	26.2	24.9
671675	24.3	28.7	26.5
671680	24.9	26.8	25.9
671682	26.8	28.6	27.7
671683	27.0	27.7	27.4
671684	25.6	27.9	26.7
671685	31.9	33.2	32.6
671689	28.6	31.1	29.9
671705	29.2	29.2	29.2
671718	16.1	26.3	21.2
671725	27.4	27.6	27.5

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC MALE RATS DURING PREMATING

GROUP: VII CONCENTRATION: 100 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	1-15
ANIMAL #			
671678	24.8	26.4	25.6
671686	27.5	29.1	28.3
671687	24.6	28.0	26.3
671691	29.4	33.1	31.2
671692	24.4	26.1	25.2
671693	24.6	26.8	25.7
671699	26.3	28.1	27.2
671702	25.6	28.8	27.2
671706	25.4	28.3	26.8
671708	29.6	29.6	29.6
671711	24.8	28.1	26.5
671722	28.2	30.0	29.1

Individual Food Consumption by Subchronic Female Rats

INDIVIDUAL FOOD CONSUMPTION BY SUBCHRONIC FEMALE RATS

EXPLANATORY NOTES

Notes

A "-" indicates that due to a technical error, food consumption was not measured during the first week of the study. As a result, food consumption for the interval of test days 1-29 could not be reported.

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC FEMALE RATS

GROUP: II CONCENTRATION: 0 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #					
671747	19.3	17.1	20.9	21.1	19.6
671758	22.0	20.0	26.8	21.0	22.5
671766	18.7	16.9	16.2	19.2	17.7
671770	17.7	17.8	15.6	20.5	17.9
671794	21.0	20.2	19.6	20.5	20.3
671799	19.0	20.4	12.5	18.4	17.6
671808	19.5	17.2	17.3	16.7	17.7
671810	19.7	20.3	19.3	19.2	19.6
671824	20.1	11.2	24.9	23.2	19.9
671828	20.1	20.7	17.3	21.9	20.0
671834	18.5	18.1	17.2	17.5	17.8
671836	-	18.6	17.1	17.3	-

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC FEMALE RATS

GROUP: IV CONCENTRATION: 5 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #					
671727	18.0	16.9	15.3	16.6	16.7
671733	19.7	16.6	18.0	21.0	18.8
671737	16.5	17.2	17.1	17.4	17.0
671742	20.6	19.4	22.7	21.7	21.1
671761	20.3	18.6	19.6	22.4	20.2
671768	22.3	20.5	20.1	20.3	20.8
671783	22.2	20.6	22.1	21.2	21.5
671788	19.6	20.0	18.1	19.9	19.4
671800	18.3	18.8	18.1	16.6	18.0
671812	15.2	16.8	16.5	16.9	16.3
671815	18.3	17.9	17.6	18.9	18.2
671825	17.5	20.0	19.0	21.6	19.5

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC FEMALE RATS

GROUP: VI CONCENTRATION: 25 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #					
671730	15.8	20.0	20.3	19.7	19.0
671739	14.7	15.5	16.4	16.1	15.7
671772	18.5	19.3	17.2	16.8	17.9
671790	19.1	19.3	21.5	19.3	19.8
671806	19.3	18.6	19.4	22.6	20.0
671814	17.8	18.3	15.9	18.5	17.6
671816	14.1	17.5	15.3	14.9	15.4
671826	20.9	20.3	18.6	19.7	19.9
671831	18.0	18.3	17.8	18.3	18.1
671832	17.0	18.9	18.2	18.1	18.1
671835	21.5	21.2	21.5	21.8	21.5
671838	17.7	14.3	14.2	15.6	15.4

INDIVIDUAL FOOD CONSUMPTION (grams/day) BY SUBCHRONIC FEMALE RATS

GROUP: VIII CONCENTRATION: 100 MG/KG/DAY

DAYS ON TEST:	1-8	8-15	15-22	22-29	1-29
ANIMAL #					
671735	20.2	16.8	15.5	15.4	17.0
671741	19.7	18.3	16.1	17.3	17.9
671748	20.0	19.9	15.7	17.5	18.3
671756	17.7	17.3	15.3	16.7	16.7
671762	23.3	20.9	20.3	20.2	21.2
671763	18.6	17.4	17.8	18.5	18.1
671767	15.8	16.5	17.6	16.2	16.5
671778	17.9	20.0	18.9	20.0	19.2
671793	16.1	18.1	18.1	19.2	17.9
671797	19.8	18.9	18.0	20.0	19.2
671811	19.5	21.2	18.9	20.5	20.0
671820	21.3	22.3	21.9	20.1	21.4

Individual Clinical Observations in Satellite Female Rats During Premating

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING

EXPLANATORY NOTES

Notes

Test Days 1-15 = Premating Period

This appendix contains data for females during the premating period. Postdosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING (PREDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671728	NO ABNORMALITIES DETECTED		
671731	NO ABNORMALITIES DETECTED		
671755	NO ABNORMALITIES DETECTED		
671776	NO ABNORMALITIES DETECTED		
671780	NO ABNORMALITIES DETECTED		
671786	NO ABNORMALITIES DETECTED		
671795	NO ABNORMALITIES DETECTED		
671798	NO ABNORMALITIES DETECTED		
671803	NO ABNORMALITIES DETECTED		
671805	NO ABNORMALITIES DETECTED		
671818	NO ABNORMALITIES DETECTED		
671822	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING (PREDOSING)

GROUP: IV-0 CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671729	ALOPECIA BOTH FRONT PAW(S)	9	15
671750	ALOPECIA BOTH FRONT PAW(S)	2	15
	ALOPECIA BOTH FRONT LEG(S)	9	15
671765	NO ABNORMALITIES DETECTED		
671779	NO ABNORMALITIES DETECTED		
671787	NO ABNORMALITIES DETECTED		
671789	NO ABNORMALITIES DETECTED		
671791	NO ABNORMALITIES DETECTED		
671792	NO ABNORMALITIES DETECTED		
671802	NO ABNORMALITIES DETECTED		
671809	NO ABNORMALITIES DETECTED		
671821	NO ABNORMALITIES DETECTED		
671830	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING (PREDOSING)

GROUP: VI-0 CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671736	NO ABNORMALITIES DETECTED		
671743	ALOPECIA NECK	5	12
	SCAB NECK	5	15
	ALOPECIA BOTH FRONT PAW(S)	10	15
	ALOPECIA BOTH FRONT LEG(S)	10	15
671746	NO ABNORMALITIES DETECTED		
671749	NO ABNORMALITIES DETECTED		
671751	ALOPECIA BOTH FRONT PAW(S)	14	15
671753	NO ABNORMALITIES DETECTED		
671754	NO ABNORMALITIES DETECTED		
671764	NO ABNORMALITIES DETECTED		
671784	NO ABNORMALITIES DETECTED		
671785	NO ABNORMALITIES DETECTED		
671829	NO ABNORMALITIES DETECTED		
671833	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING (PREDOSING)

GROUP: VIII-0 CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671745	NO ABNORMALITIES DETECTED		
671752	NO ABNORMALITIES DETECTED		
671760	NO ABNORMALITIES DETECTED		
671771	NO ABNORMALITIES DETECTED		
671777	ALOPECIA LEFT FRONT LEG(S)	9	9
	ALOPECIA BOTH FRONT LEG(S)	10	15
671782	NO ABNORMALITIES DETECTED		
671804	NO ABNORMALITIES DETECTED		
671807	ALOPECIA BOTH FRONT PAW(S)	9	15
	ALOPECIA BOTH FRONT LEG(S)	10	15
671813	NO ABNORMALITIES DETECTED		
671817	NO ABNORMALITIES DETECTED		
671819	NO ABNORMALITIES DETECTED		
671823	NO ABNORMALITIES DETECTED		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING (POSTDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671728	-		
671731	-		
671755	-		
671776	-		
671780	-		
671786	-		
671795	-		
671798	-		
671803	-		
671805	-		
671818	-		
671822	-		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING (POSTDOSING)

GROUP: IV-0 CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671729	-		
671750	-		
671765	-		
671779	-		
671787	-		
671789	-		
671791	-		
671792	-		
671802	-		
671809	-		
671821	-		
671830	-		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING (POSTDOSING)

GROUP: VI-0 CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671736	-		
671743	-		
671746	-		
671749	-		
671751	-		
671753	-		
671754	-		
671764	-		
671784	-		
671785	-		
671829	-		
671833	-		

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING PREMATING (POSTDOSING)

GROUP: VIII-0 CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671745	-		
671752	-		
671760	-		
671771	COLORED DISCHARGE LEFT EYE(S) RED	1	1
	COLORED DISCHARGE LEFT EYE(S) RED	3	3
671777	-		
671782	-		
671804	-		
671807	-		
671813	-		
671817	-		
671819	-		
671823	-		

Individual Clinical Observations in Satellite Female Rats During Gestation

INDIVIDUAL CLINICAL OBSERVATIONS IN SATELLITE FEMALE RATS
DURING GESTATION

EXPLANATORY NOTES

Note

This Appendix contains data from females with evidence of copulation observed (gestation days 0-21).

Postdosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671728	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671731	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671755	VAGINAL PLUG	0	0
671780	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671786	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671798	VAGINAL PLUG	0	0
	ALOPECIA BOTH FRONT PAW(S)	5	21
671803	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA CHEST	17	18
	ALOPECIA UNDERBODY	19	21
671805	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671818	VAGINAL PLUG	0	0
671822	VAGINAL PLUG	0	0

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

GROUP: IV-0 CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671729	ALOPECIA BOTH FRONT PAW(S)	0	21
	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671750	ALOPECIA BOTH FRONT PAW(S)	0	21
	ALOPECIA BOTH FRONT LEG(S)	0	21
	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA RIGHT REAR LEG(S)	8	21
	ALOPECIA CHEST	11	21
671765	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA BOTH FRONT PAW(S)	4	21
	ALOPECIA BOTH FRONT LEG(S)	4	21
671779	VAGINAL PLUG	0	0
671787	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671789	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671791	VAGINAL PLUG	0	0
671792	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA BOTH FRONT PAW(S)	18	21
671802	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671809	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671821	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671830	VAGINAL PLUG	0	0

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

GROUP: VI-0 CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671736	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA BOTH FRONT PAW(S)	17	21
671743	SCAB NECK	0	6
	ALOPECIA BOTH FRONT PAW(S)	0	21
	ALOPECIA BOTH FRONT LEG(S)	0	21
	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671746	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671749	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671751	ALOPECIA BOTH FRONT PAW(S)	0	21
	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671753	VAGINAL PLUG	0	0
671754	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671764	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA BOTH FRONT LEG(S)	19	21
671784	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671785	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA BOTH FRONT PAW(S)	15	21
671829	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671833	VAGINAL PLUG	0	0

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (PREDOSING)

GROUP: VIII-0 CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671745	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671752	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671760	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA LEFT FRONT PAW(S)	1	5
671771	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	COLORED DISCHARGE LEFT EYE(S) RED	9	11
	SORE FACE	20	21
671777	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	ALOPECIA BOTH FRONT LEG(S)	0	25
	ALOPECIA BOTH FRONT PAW(S)	1	25
671782	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671804	VAGINAL PLUG	0	0
671807	ALOPECIA BOTH FRONT PAW(S)	0	21
	ALOPECIA BOTH FRONT LEG(S)	0	21
	VAGINAL PLUG	0	0
671813	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
	SALIVATION	5	5
671817	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671819	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0
671823	CAGEBOARD PLUGS	0	0
	SPERM POSITIVE	0	0

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671728	-		
671731	-		
671755	-		
671780	-		
671786	-		
671798	-		
671803	-		
671805	-		
671818	-		
671822	-		

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

GROUP: IV-0 CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671729	-		
671750	-		
671765	-		
671779	-		
671787	-		
671789	-		
671791	-		
671792	-		
671802	-		
671809	-		
671821	-		
671830	-		

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

GROUP: VI-0 CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671736	-		
671743	-		
671746	-		
671749	-		
671751	-		
671753	-		
671754	-		
671764	-		
671784	-		
671785	-		
671829	-		
671833	-		

INDIVIDUAL CLINICAL OBSERVATIONS
IN SATELLITE FEMALE RATS DURING GESTATION (POSTDOSING)

GROUP: VIII-0 CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671752	-		
671745	-		
671760	-		
671771	SORE FACE	19	19
671777	-		
671782	-		
671804	-		
671807	-		
671813	SALIVATION	5	8
671817	-		
671819	-		
671823	-		

**Individual Clinical Observations and Mortality Data
in Satellite Female Rats During Lactation**

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION

EXPLANATORY NOTES

Notes

Test days for animal fates are determined from the initiation of test substance administration.

This appendix contains data from females that delivered a litter (lactation days 0-4).

Postdosing clinical observations were recorded by exception. A "-" indicates that no signs were present for a given animal.

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671728	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		
671731	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 44		
671755	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
671780	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
671786	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 43		
671798	ALOPECIA BOTH FRONT PAW(S) SACRIFICED BY DESIGN TEST DAY 42	0	4
671803	ALOPECIA UNDERBODY SACRIFICED BY DESIGN TEST DAY 45	0	4
671805	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 46		
671818	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 42		
671822	NO ABNORMALITIES DETECTED SACRIFICED BY DESIGN TEST DAY 45		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

GROUP: IV-0 CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671729	ALOPECIA BOTH FRONT PAW(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 45		
671750	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	0	4
	ALOPECIA RIGHT REAR LEG(S)	0	4
	ALOPECIA CHEST	0	4
	SACRIFICED BY DESIGN TEST DAY 51		
671765	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 42		
671779	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		
671787	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		
671789	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 44		
671791	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 45		
671792	ALOPECIA BOTH FRONT PAW(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 44		
671802	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 46		
671809	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 49		
671821	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
671830	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 42		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

GROUP: VI-0 CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671736	ALOPECIA BOTH FRONT PAW(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 43		
671743	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 42		
671746	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
671751	ALOPECIA BOTH FRONT PAW(S)	0	2
	SACRIFICED BY DESIGN TEST DAY 54		
671753	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
671754	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
671764	ALOPECIA BOTH FRONT LEG(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 45		
671784	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 42		
671785	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	1	4
	SACRIFICED BY DESIGN TEST DAY 42		
671829	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 46		
671833	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (PREDOSING)

GROUP: VIII-0 CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671745	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 46		
671760	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 44		
671771	SORE FACE	0	4
	ALOPECIA BOTH FRONT PAW(S)	2	4
	SACRIFICED BY DESIGN TEST DAY 44		
671782	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		
671804	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 42		
671807	ALOPECIA BOTH FRONT PAW(S)	0	4
	ALOPECIA BOTH FRONT LEG(S)	0	4
	SACRIFICED BY DESIGN TEST DAY 46		
671813	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 42		
671817	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 42		
671819	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 44		
671823	NO ABNORMALITIES DETECTED		
	SACRIFICED BY DESIGN TEST DAY 43		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

GROUP: II-0 CONCENTRATION: 0 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671728	-		
671731	-		
671755	-		
671780	-		
671786	-		
671798	-		
671803	-		
671805	-		
671818	-		
671822	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

GROUP: IV-0 CONCENTRATION: 5 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671729	-		
671750	-		
671765	-		
671779	-		
671787	-		
671789	-		
671791	-		
671792	-		
671802	-		
671809	-		
671821	-		
671830	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

GROUP: VI-0 CONCENTRATION: 25 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671736	-		
671743	-		
671746	-		
671751	-		
671753	-		
671754	-		
671764	-		
671784	-		
671785	-		
671829	-		
671833	-		

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY DATA
IN SATELLITE FEMALE RATS DURING LACTATION (POSTDOSING)

GROUP: VIII-0 CONCENTRATION: 100 MG/KG/DAY

ANIMAL NUMBER	OBSERVATION	FIRST DAY OBSERVED	LAST DAY OBSERVED
671745	-		
671760	-		
671771	-		
671782	-		
671804	-		
671807	-		
671813	-		
671817	-		
671819	-		
671823	-		